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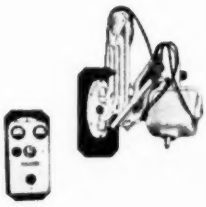

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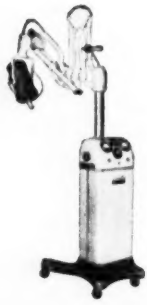

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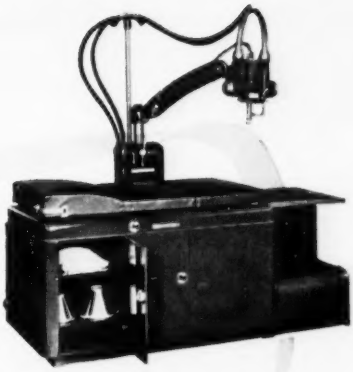

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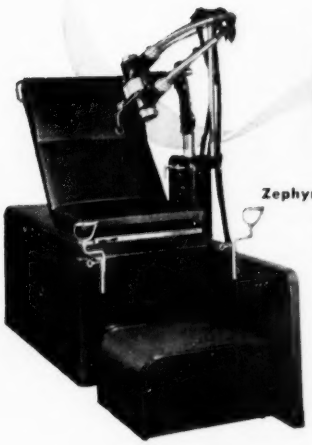

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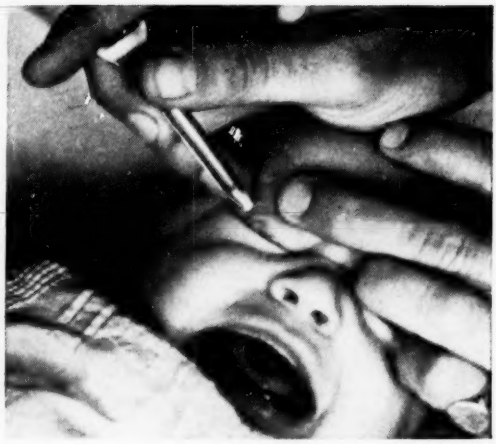

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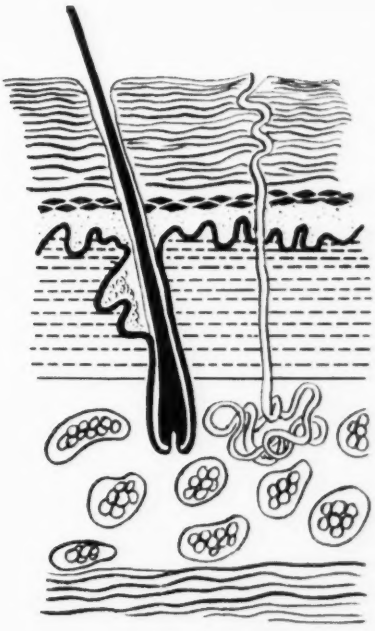

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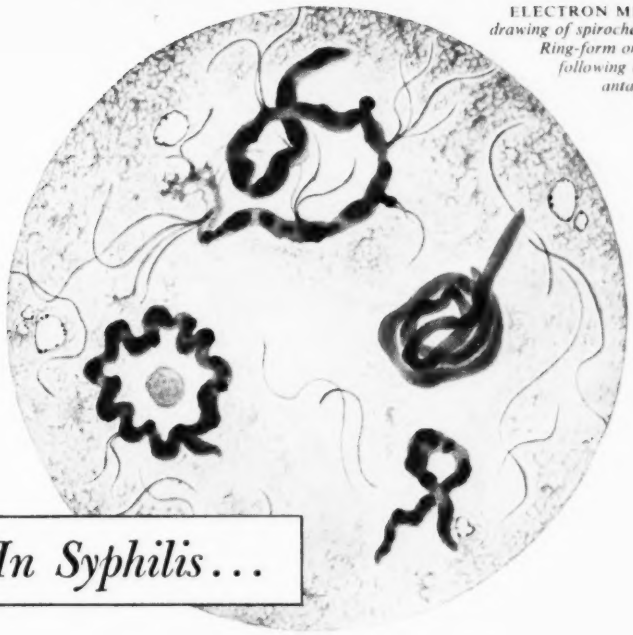

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VOLUME 68 SEPTEMBER 1953 NUMBER 3

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CHONDRODERMATITIS NODULARIS CHRONICA HELICIS

Report of Ninety-Four Cases and Survey of Literature, with Emphasis upon Pathogenesis and Treatment

VICTOR D. NEWCOMER, M.D.
CHARLES GEORGE STEFFEN, M.D.
THOMAS H. STERNBERG, M.D.
AND
LOUIS LICHTENSTEIN, M.D.
LOS ANGELES

THE PURPOSE of this paper is to report a survey of 94 cases of chondrodermatitis nodularis chronica helicis observed at this center over a period of six years and to present our concept of the pathogenesis and treatment of this condition.

REVIEW OF THE LITERATURE

Clinical Description.—Winkler,[1] in 1916, first described this condition under the title mentioned and presented eight cases. It was his impression that it represented an entity, and he characterized it as a small painful nodule on the ear, having a distinctive pathologic picture. The helix, specifically, was the site of involvement in all his cases. The lesions were "cherry seed" in size and had a firmly attached, centrally located crust. Intense pain was elicited when he attempted to remove this crust, and its removal revealed a small, well-defined ulcer with an erythematous base. The remainder of the nodule was the color of the surrounding skin or a shade lighter and was translucent. The lesion was immovable on its base. Episodes of inflammation and drainage of a purulent exudate from beneath the crust were observed. The patient experienced intense pain at such times, particularly when he lay on the involved ear. Spontaneous cures were not observed, but remissions did occur, which lasted as long as several years.

Foerster [2] also described the condition, apparently independently, in 1918. His clinical description [3] and that of subsequent investigators [4] corresponded in general to that of Winkler.

From the Veterans Administration Center and the Division of Dermatology, Department of Medicine, University of California Medical Center.

Illustrations are through the courtesy of the Medical Illustration Laboratory, Veterans Administration Center, Los Angeles 25, William L. M. Martinsen, F.B.P.A., Director.

1. Winkler, M.: Chondrodermatitis Nodularis Chronica Helicis, Arch. Dermat. u. Syph. **121**:278, 1916.

2. Foerster, O. H.: Painful Nodular Growth of the Ear, J. Cutan. Dis. **36**:154, 1918.

3. Foerster, O. H.: Painful Nodular Growth of the Ear, Arch. Dermat. & Syph. **11**:149, 1925; footnote 2.

(Footnotes continued on next page)

Location, Sex, and Age Incidence.—The helix, as noted, is characteristically the site of involvement, the right much more frequently than the left.[4h] Occasionally chondrodermatitis nodularis chronica helicis is observed on the antihelix, particularly in women.[5] Klauder [6] did not accept such nodules on the antihelix in women as true instances of chondrodermatitis nodularis chronica helicis, although his viewpoint has found little support from subsequent investigators.[7]

The original observers [8] described the condition as occurring exclusively in males. Duncan,[5a] however, reviewing the literature in 1937 regarding this point, found that approximately 10% of the recorded cases had occurred in women. As for race incidence, it may be stated that there have been no instances reported in Negros, at least in the literature available to us. There is general agreement that the lesion is essentially one of middle and advanced age. Only 3 patients among 26 reported on by Culver [4f] and no more than 2 patients in Ebenius' series of 33 were younger than 40. It should be noted, however, that the condition has been recorded [7] in patients as young as 20 years.

Pathogenesis.—Trauma of various types has been considered to be the primary etiological factor in initiating this condition. Trauma to the helix as a result of wearing a hat has been suggested as explaining the higher incidence in men,[4d] and, in particular, Duncan [5a] felt that the longer hair of women offered them protection from trauma of this type. The wearing of occupational headgear, such as telephone operators' earphones, nuns' coifs, and soldiers' helmets, has likewise been considered to have etiological significance. It is noteworthy, also, that Ebenius [4h] elicited a history of frostbite in 50% of a series of 26 cases and felt that there was a definite relationship between frostbite and this disease. He regarded prolonged pressure on the ear during sleep as another important factor and explained the greater incidence of right-sided involvement as being due to the fact that most people sleep on that side.

Degenerative changes of the auricular cartilage have also been held to initiate the changes in chondrodermatitis nodularis chronica helicis. This view dates back to Winkler,[1] who believed that the auricular cartilage had been damaged by trau-

4. (*a*) Mitchell, J. H.: Chondrodermatitis Nodularis Helicis, Arch. Dermat. & Syph. **7**:132, 1923. (*b*) Dubreuilh, W., and Pigeard de Gurbert, M.: Nodule douloureux de l'oreille, Ann. dermat. et syph. **9**:729, 1928. (*c*) Davies, J. H. T.: Chondrodermatitis Nodularis Chronica Helicis, Rev. franç. de dermat. et de vénéréol. **4**:388, 1928. (*d*) Fox, H.: Chondrodermatitis Nodularis Chronica Helicis, Arch. Dermat. & Syph. **19**:1016, 1929. (*e*) Belgodère, G.: Nodule douloureux de l'oreille, Ann. dermat. et syph. **10**:873, 1929. (*f*) Culver, G. D.: Painful Ear Nodule of Winkler and Foerster: Report of Cases, California & West. Med. **31**:414, 1929. (*g*) Nicolas, J.; Massia, G., and Colas, J.: Nouveau cas de nodule douloureux de l'oreille, Bull. Soc. franç. dermat. et syph. **43**:1437, 1936. (*h*) Ebenius, B.: Chondrodermatitis Chronica Auriculae, Acta radiol. **22**:563, 1941.

5. (*a*) Duncan, O.: Sex Incidence of Chondrodermatitis Nodularis Chronica Helicis, Texas J. Med. **33**:19, 1937. (*b*) Jaenicke, K.: Chondrodermatitis Nodularis Chronica Helicis, Arch. Dermat. & Syph. **43**:158, 1941. (*c*) Fox.[4d]

6. Klauder, J. V.: Nodule of Ear Simulating Chondrodermatitis Nodularis Chronica Helicis, Arch. Dermat. & Syph. **22**:833, 1930.

7. Culver.[4f] Ebenius.[4h] Duncan.[5a]

8. Winkler.[1] Foerster.[2]

matic, chemical, or thermal influences to the extent that it acted as a foreign body provoking a chronic inflammatory reaction. Foerster [3] agreed, in general, with this viewpoint. Halter [9] stated that the cartilage of the helix was predisposed to the development of this disease because of its peculiar anatomical position. He pointed out that this, combined with a prolonged interference of the blood supply, produced a locus minoris resistentiae readily subject to injury by trauma. Other theories regarding the pathogenesis of chondrodermatitis nodularis chronica helicis have been proposed. Carol and van Haren [10] did not feel that the cartilage plays a primary role, but rather that the epidermis is the site of the initial lesion, the changes in the cutis being secondary. Still other theories are that the lesion represents an angiokeratoma and that it resembles the glomus tumor of Masson.[4g]

Treatment.—Many modalities of therapy have been used. These include roentgen therapy, use of radium, applications of carbon dioxide snow or trichloroacetic acid, desiccation and curettage, and excision. The accrued clinical reports would

TABLE 1.—*Histopathological Diagnoses of All Biopsy Specimens Obtained from Ear in Dermatology Department from 1946 to 1951, Inclusive*

Diagnosis	No. of Cases
Chondrodermatitis nodularis chronica helicis	69
Squamous cell carcinoma	43
Senile keratosis	27
Basal cell carcinoma	20
Sebaceous cyst	4
Benign keratosis	3
Nevus	3
Chronic inflammation	2
Squamous cell papilloma	2
Basal-squamous cell carcinoma	2
Lupus erythematosus	2
Sebaceous papilloma	1
Lipoma	1
Nonspecific dermatitis	1

indicate that wide excision including the involved portion of the cartilage gives the most satisfactory results.[11] Nelson [12] recently treated nine patients by the application of bacitracin ointment (Baciguent) and noted clinical remission in eight. Altogether, despite some optimistic reports, no method of treatment to date has proved entirely satisfactory (Table 6).

CLINICAL ANALYSIS OF MATERIAL

Between 1946 and 1951 there were 180 patients in our clinic who presented auricular lesions which were biopsied. The incidence of chondrodermatitis nodularis chronica helicis among them was 39%, making this the most commonly biopsied condition of the external ear observed in the dermatology service. The pathologic diagnoses established are indicated in Table 1.

9. Halter, K.: Zur Pathogenese der Chondrodermatitis nodularis chronica helicis, Dermat. Ztschr. **73**:270, 1936.

10. Carol, W. L. L., and van Haren, H. B.: Über Clavus helicis bzw. Chondrodermatitis nodularis chronica helicis, Dermatologica **83**:353, 1941.

11. Foerster,[3] Dubreuilh and Pigeard de Gurbert,[4b] Culver,[4f] Ebenius,[4h] Roxburgh, A. C.: Chondro-Dermatitis Nodularis Chronica Helicis, Brit. J. Dermat. **39**:112, 1927.

12. Nelson, L. M.: Chondrodermatitis Nodularis Chronica Helicis: Treatment with Bacitracin Ointment, Arch. Dermat. & Syph. **65**:356, 1952.

As noted, the condition is predominantly one of middle and old age (Table 2). The youngest in our series of patients was 27; the oldest was 85. It is significant that 95% were between 50 and 80. No nationality was predominant. All our patients were white with the exception of a 27-year-old Negro, who had progressive generalized scleroderma with involvement also of the ears. Painful nodules developed on both helices in this patient. These were surgically removed and proved to be lesions of chondrodermatitis nodularis chronica helicis. Incidentally, both lesions recurred.

The occupations of this group varied widely, and there was no apparent correlation between any particular occupation and the development of the condition. It may be significant, however, that approximately two-thirds of the patients had been employed for long periods in positions in which sun exposure was a daily occurrence.

Pain or tenderness was the initial and chief complaint in every case. Generally, it was first noted to occur at night. Many patients were unable to sleep on the

TABLE 2.—*Ages of Patients with Chondrodermatitis Nodularis Chronica Helicis*

Age, Yr.	No. of Patients	Age, Yr.	No. of Patients
20-30	1	60-70	22
30-40	1	70-80	12
40-50	1	80-90	1
50-60	31		

TABLE 3.—*Anatomical Location of Chondrodermatitis Nodularis Chronica Helicis*

Location	No. of Cases	Location	No. of Cases
Helix		Antihelix	
Left	23	Left	3
Right	34	Right	5
Bilateral	4		

affected side because of intense knife-like pain. The nodule became increasingly tender and more painful until the patients sought therapy. Symptoms had been present for approximately two months in the majority of patients. In several instances, however, the disease had been present for a number of years, during which time there had been many spontaneous exacerbations and remissions.

The appearance of the nodules, as we observed them, corresponded closely to Winkler's original description. Figure 1 illustrates the clinical appearance of typical lesions. Central ulceration was observed in 15 of the 69 patients. A history of ulceration and drainage, however, could frequently be obtained. The helix of the right ear, as indicated, is the commoner location, but the helix of the left ear is frequently involved (Table 3).

The majority of the patients, being older persons, had concomitant systemic disease of one type or another. The systemic disabilities were charted to determine whether there might be any underlying predisposing cause of chondrodermatitis nodularis chronica helicis. Table 4 lists the various systemic diseases encountered and the frequency of each observed in this group of patients. The only condition occurring with significant frequency is arteriosclerotic heart disease, and this probably reflects nothing more than the mean age of the group.

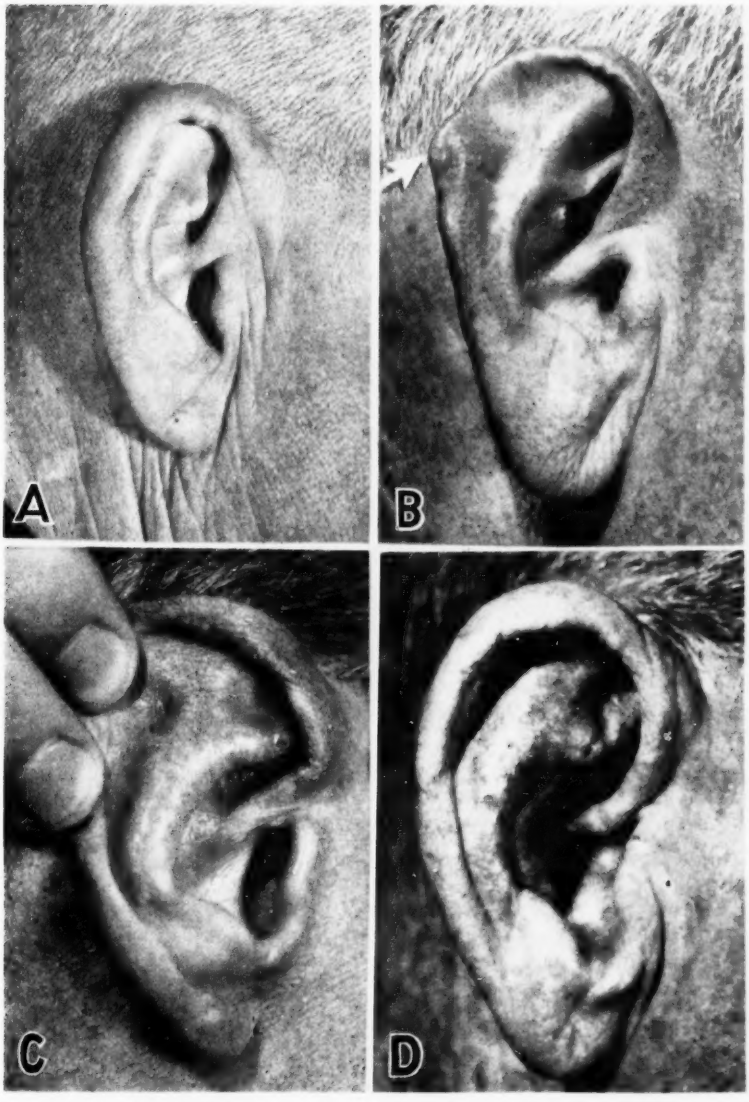

Fig. 1.—*A*, typical lesion and site of chondrodermatitis nodularis chronica helicis. *B*, recurrence of chondrodermatitis nodularis chronica helicis following surgical excision. Loss of rim of helix is due to two previous attempts to eradicate the disease. *C*, chondrodermatitis nodularis chronica helicis on both antihelix and opposing rim of helix in a patient who, because of a physical disability, was forced to sleep on involved side. *D*, chondrodermatitis nodularis chronica helicis on antihelix.

PATHOLOGIC CHANGES OBSERVED IN SURGICAL SPECIMENS

The following composite description may serve to characterize the essential pathologic changes of chondrodermatitis nodularis chronica helicis. In well-oriented sections one commonly observes a small central area of necrosis of the epidermis and, not infrequently, ulceration as well. The crust over this area of necrosis, when present, is composed, as a rule, of parakeratotic scales, along with extravasated blood and often polymorphonuclear leucocytes. There are usually reactive thickening, hyperkeratosis, and acanthosis of the epidermis surrounding this focus. The base of an active ulcer is likely to be composed of polymorphonuclear leucocytes, organizing fibrin, and extravasated blood. Beneath this, extending into the "nodule" and downward, frequently, to the perichondrium, one observes inflamed granulation tissue, rich in small vessels and capillaries, which may show active reticuloendothelial hyperplasia and mobilization of histiocytes. There may even be superficial erosion of the cartilage by this granulation tissue. It should also be noted that organizing

TABLE 4.—*Systemic Diagnoses for Patients with Chondrodermatitis Nodularis Chronica Helicis**

Disease	No. of Patients
Arteriosclerotic heart disease	22
Hypertensive cardiovascular disease	6
Pulmonary tuberculosis	4
Bronchitis	4
Duodenal ulcer	4
Arthritis, hypertrophic	4
Syphilis, central nervous system	3
Alcoholism	3
Cirrhosis, hepatic	3
Diabetes mellitus	2
Arthritis, rheumatoid	2
Paget's disease of skull	1
Encephalitis, alcoholic	1
Schizophrenia	1
Syphilis, late latent	1
Scleroderma	1
Pernicious anemia	1
No systemic diagnosis	36

* Several patients had more than one systemic disease.

granulation tissue and scar tissue tend to envelop small nerve bundles within the perichondrium or its proximity, and this may be responsible for much of the pain associated with the lesion. In older lesions one observes more fibroblastic proliferation as an expression of repair, as well as a more chronic type of inflammatory infiltrate, characterized by the presence of lymphocytes, plasma cells, and mononuclear macrophages.

In addition, one notes, of course, the usual senescent changes in the cutis and in the auricular cartilage as well. In the cutis these are especially of the nature of basophilic degeneration, senile elastosis, and thickening of arteriolar walls. In the cartilage of the ear one observed in many instances, in addition to the superficial erosion previously noted, more or less pronounced regressive changes. Specifically, the outer portion of the cartilage, and sometimes also the central portion, frequently shows alteration of its basophilic chondroid matrix in the direction of fibrous dedifferentiation and, concomitantly, focal disappearance of the cartilage cells. As a consequence, the auricular cartilage may acquire a smudgy, hyaline, ill-defined contour, particularly on its outer or superficial face. Otherwise, one commonly

observes irregular calcification of cartilage cells and their matrix, as another expression of physiologic aging. It must be emphasized, however, that the changes described vary in extent from case to case and are not necessarily confined to the cartilage zone directly beneath the cutaneous lesion. In fact, they appear to be distributed unevenly throughout the entire sample of auricular cartilage and bear no specific relationship to the localized inflammatory field. In this connection, it may be noted further that, in some instances, the cartilage of the ear presents a relatively normal appearance, despite the intense inflammatory reaction adjacent to it. This general description of the essential changes seen in biopsy material is essentially in accord with that in the literature.[13]

CONTROL GROUP

It was our feeling that study of an adequate control group was indicated because of the etiological significance commonly ascribed to changes in the auricular cartilage and the fact that we could not correlate these changes directly with chondrodermatitis nodularis chronica helicis. Specifically, the microscopic appearance of normal auricular cartilage was studied in those age groups in which chondrodermatitis

TABLE 5.—*Ages of Subjects Used as Controls*

Age, Yr.	No. of Controls	Age, Yr.	No. of Controls
20-30	1	60-70	4
30-40	3	70-80	3
40-50	4	80-	1
50-60	4		

nodularis chronica helicis was most frequently found. The study was done in the following manner:

Large sections of cartilage were excised at autopsy from the tip of the helix of 20 subjects whose ages varied from 28 to 83 years (Table 5). Nineteen of the twenty were men. In no instance was there any known disease of the ear prior to death. The sections of cartilage were processed in the usual manner and stained with hematoxylin and eosin.

The microscopic findings in these sections of cartilage varied greatly, as one might expect, depending upon the age of the subject. The architecture in the specimens obtained from subjects below the age of 40 corresponded to that which is described as normal for the human ear.[14] The auricular cartilage is of the elastic variety. It presents a coarse-appearing ground substance throughout the central areas. Peripherally, the coarseness is less evident and one observes a more homogeneous appearance. There is also a difference in staining properties between the

13. Rost, G. A.: Chondrodermatitis nodularis chronica helicis, Wein. med. Wchnschr. **76**:931, 1926. Meirowsky, E.: Zur Kenntnis der sogenannten Chondrodermatitis nodularis chronica helicis, Dermat. Wchnschr. **88**:289, 1929. Winkler,[1] Foerster,[3] Mitchell,[4a] Nicolas and others,[4g] Ebenius,[4h] Halter,[9] Carol and van Haren.[10]

14. Ramón y Cajal, S.: Histology, revised by J. F. Tello-Múñoz, translated by M. Fernan-Núñiz, Baltimore, William Wood & Company, 1933. Smith, P. E., and others, Editors: Bailey's Textbook of Histology, Ed. 10, Baltimore, William Wood & Company, 1940. Maksimov, A. A., and Bloom, W.: Textbook of Histology, Ed. 4, Philadelphia, W. B. Saunders Company, 1942. Jordan, H. E.: A Textbook of Histology, Ed. 8, D. Appleton-Century Company, Inc., 1947.

Fig. 2.—*A*, low-power photomicrograph of representative lesion of chondrodermatitis nodularis chronica helicis demonstrating focal ulceration, acanthotic proliferation of epidermis at borders of ulcer, and central area of necrosis in cutis surrounded by intense lymphocytic and epithelioid cell infiltrate; × 18. *B*, photomicrograph of auricular lesion of chondrodermatitis nodularis chronica helicis demonstrating in upper left field frequently observed degenerative changes in cutis seen in association with this disease; × 24.

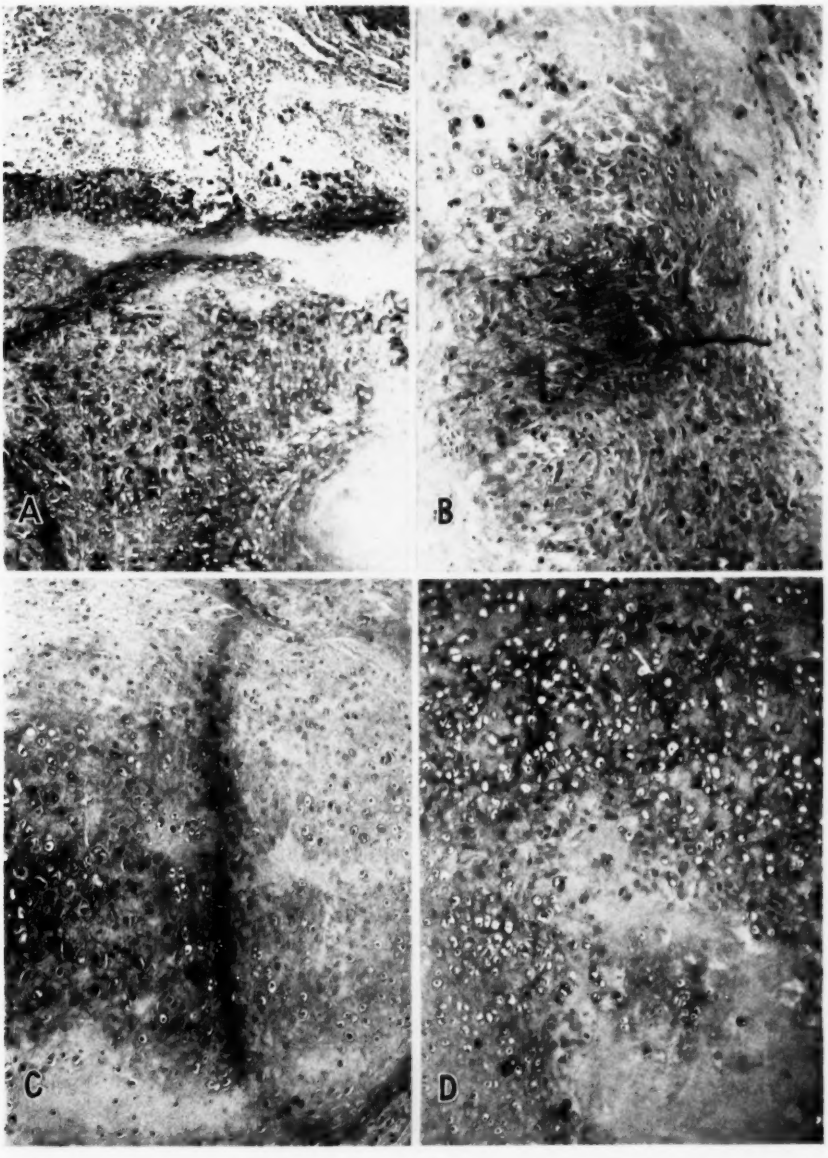

Fig. 3.—*A*, field of auricular cartilage in lesion of chondrodermatitis nodularis chronica helicis demonstrating fibrillation of cartilage matrix with zones of peripheral and central hyalinization. (These degenerative changes have in past been thought to have etiological significance in development of the disease.) × about 53. *B*, similar fibrillar pattern observed in "normal" control cartilage obtained from man aged 72; × about 53. *C*, auricular cartilage from another lesion of chondrodermatitis nodularis chronica helicis showing vacuolization of cartilage cells and hyalinization of matrix; × about 53. *D*, comparable degenerative changes in "normal" control cartilage obtained from man aged 65; × about 53.

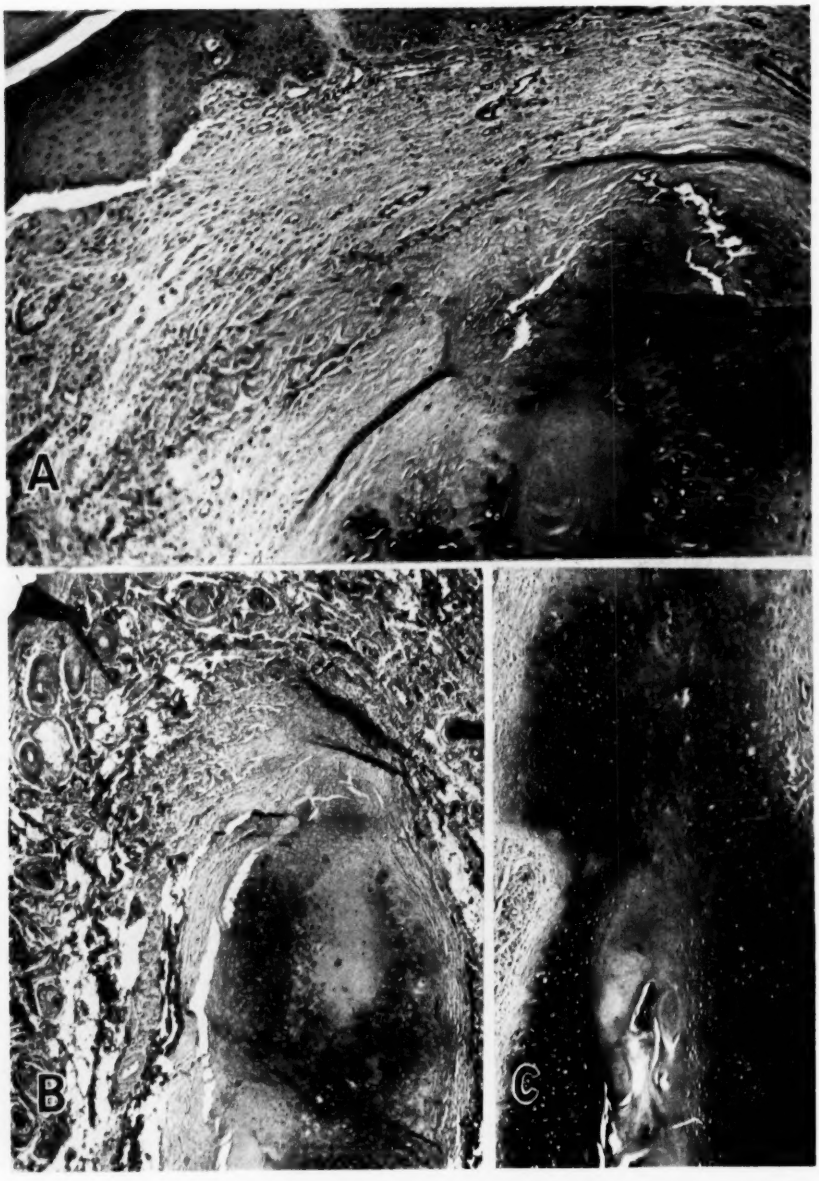

Fig. 4.—*A*, hyalinization in apex of cartilage in chrondrodermatitis nodularis chronica helicis. This degenerative change has frequently been singled out as initiating factor of condition. × 24. *B*, comparable hyalinization in "normal" control cartilage obtained from man aged 63; × 18. *C*, advanced hyalinization with early calcium deposition in "normal" control cartilage obtained from man aged 71; × 18.

central portion and the periphery. The large central area is basophilic and takes a purple hue when stained with hematoxylin and eosin. This, in turn, merges abruptly with a narrow eosinophilic cartilaginous periphery, which, in turn, blends with the perichondrium. The width of the eosinophilic margin and of the basophilic central area is constant throughout the section. The lacunae are usually paired and contain the cartilage cells. These cells can be clearly seen and contain a network-like cytoplasm in which the nucleus is placed peripherally. The lacunae are smaller and flattened at the cartilaginous margin, and the cell nuclei here occupy a central position. The perichondrium consists of a fibrous covering, which is eosinophilic and rather acellular. Its fibers appear wavy and are arranged parallel to the cartilage surface. They blend with the cartilage on one side and with the deep cutis on the other.

Definite changes were observed, however, in the microscopic appearance and staining properties of the cartilage after the age of 40 (Figs. 2, 3, and 4). These became increasingly frequent and more extensive as advancing age groups were studied. One of the first and most frequent changes noted was in the uniformity of the basophilic cartilaginous matrix. This was modified by the presence of focal eosinophilic hyalinization resulting in ill-defined plaques, showing complete disappearance of the chondrocytes and their lacunae. The matrix in these areas was of an amorphous homogeneous nature. At the junction between the eosinophilic plaques and the normal cartilage, wavy bundles of eosinophilic strands were found. These emerged from the structure of the normal cartilage and extended into the eosinophilic areas. Small deposits of calcium were also noted in some sections. It was noted further that cartilage cells and lacunae become larger and more widely separated with advancing age. In some instances the cells had completely disappeared from the lacunae. The peripheral portion of the cartilage, in particular, became increasingly acellular and eventually rather amorphous in appearance.

The perichondrium also undergoes changes in the older age groups. Its fine fibrillar structure is lost, its cells disappear, and it is finally replaced by a wide eosinophilic band. Altogether, these observations cast considerable doubt upon the etiological significance of the comparable changes in the auricular cartilage commonly described in cases of chondrodermatitis nodularis chronica helicis.

TREATMENT

Surgery.—The recommended modality of therapy for this condition at the present time is surgical excision of the nodule with removal also of an adequate portion of the underlying cartilage. The rationale for the removal of this segment of cartilage is based on the premise that the disease has its origin in this site and that recurrence would therefore follow if the involved portion of the cartilage were not included in the excision of the lesion.

Following this accepted practice, we employed wide surgical excision of the nodule and the underlying cartilage in the treatment of 69 patients with chondrodermatitis nodularis chronica helicis during a five-year period terminating in 1951. We recently reevaluated 58 of the cases for the purpose of this study. Eighteen patients had had a recurrence of the lesion within two months to three years after the original excision. Recurrences were commonest (12 patients) during the first

year after surgery. Surgical excision was performed on 12 of the 18 lesions which recurred. The disease again developed in five of the patients. All five underwent a third excision, and the disease has reappeared in three to date. Recurrences following surgery were frequently characterized by two painful nodules, one at each end of the excision.

The reappearance of the condition following operation was actually more frequent than the figures would indicate. Many of our patients gave a history and showed clinical evidence of surgical removal of the nodule prior to the initial excision by us. Larger sections of the auricular cartilage were removed at the time of operation during the last year of the series in an attempt to lower the incidence of recurrences. As noted, our rationale for this procedure was based on the current opinion that

TABLE 6.—*Various Modalities Employed in Treatment of Chondrodermatitis Nodularis Chronica Helicis and Summary of Results*

	Cases Collected from Literature (91)	Cases in Present Series (94)
Excision	45	69
Patient followed	..	58
Recurrences	20	18
Percentage not benefited	44	31
Electrosurgery	16	..
Recurrences	6	..
Percentage not benefited	38	..
Radium	11	..
No benefit	1	..
Recurrences	4	..
Percentage not benefited	44	..
Roentgen therapy	10	..
No benefit	3	..
Recurrences	5	..
Percentage not benefited	80	..
Trichloroacetic acid	1	..
Recurrences	1	..
Percentage not benefited	100	..
Bacitracin ointment	9	8
No benefit	1	5
Percentage not benefited	11	63
Procaine injections	..	17
No benefit	..	6
Percentage not benefited	..	35

degenerative changes in the cartilage play a major role in the disease process. The incidence of recurrence, however, was not reduced by this procedure. Table 6 summarizes the results of the various therapeutic procedures which have been employed in the treatment of chondrodermatitis nodularis chronica helicis to the present time.

Procaine Injections.—Other therapeutic approaches seemed worthy of investigation in view of this failure rate and the objectionable cosmetic results associated with surgical excision of chondrodermatitis nodularis chronica helicis. A solution of procaine hydrochloride was injected into the helix of the ear in an effort to relieve the pain and perhaps stimulate healing of the focal area of necrosis in the cutis. A daily dose of 0.5 to 1.0 cc. of a 2% solution was injected subcutaneously into and around the nodule. Injections were given daily for seven days. Nine patients have been thus treated to date. Seven patients were temporarily cured, but in two of this group recurrences subsequently developed. Two were not benefited.

In eight patients, the nodules were injected locally with 0.5 to 1.0 cc. of a solution containing 2% procaine hydrochloride combined with a 1:1,000 solution of

histamine sulfate. The histamine sulfate was added in an effort to increase the vascularity in and around the lesion. Daily injections were given for seven days, the procedure as described being employed. Two of these patients derived no benefit; six were cured, without relapse to date.

Ointment.—Eight patients were given bacitracin ointment to apply locally, as suggested by Nelson.[12] They were instructed to apply the ointment to the lesion three times a day. Their condition was evaluated at the end of two months. Three experienced subjective improvement to the extent that they wished to continue the applications. There was no change of symptoms, however, in the remaining five patients.

COMMENT

Chondrodermatitis nodularis chronica helicis is a commoner condition than the reports in the literature would indicate. It was found to be the most frequently encountered disease of the external ear seen in the dermatology service at this institution, which cares for male veterans predominantly.

The disease has very definite clinical characteristics already indicated. A biopsy is rarely necessary to confirm the diagnosis when these are present. Malignant change has never been reported to our knowledge. However, a biopsy should be performed if there is any serious doubt as to the diagnosis.

All investigators, with the exception of Carol and van Haren,[10] have agreed with Winkler [1] that degenerative changes of the cartilage initiate and play an important role in the pathogenesis of this condition. We do not concur in this opinion for several reasons. Firstly, all the changes in the cartilage described in association with chondrodermatitis nodularis chronica helicis were found in auricular cartilage obtained at autopsy from subjects of the same age groups. As noted, none of these subjects had had known auricular pathology prior to death, in spite of the fact that in many instances the cartilage obtained from them revealed more extensive degenerative changes than those seen in chondrodermatitis nodularis chronica helicis. Secondly, the areas of degeneration of the cartilage beneath the nodule often did not correspond to the site of the inflammatory reaction in the cutis. As indicated, degenerative changes were frequently observed throughout the entire section and appeared to have little relationship to the changes in the cutis. Moreover, in some of the patients with chondrodermatitis nodularis chronica helicis the cartilage appeared relatively normal. Finally, in all patients the cutis was the site of the greatest pathologic changes.

As noted, Carol and van Haren have also questioned the etiological role of the auricular cartilage in this disease process. These investigators examined four nodules serially and concluded that the epidermis was the site of origin of the disease. They felt that the nodule was an ordinary clavus, differing only in its characteristic location, and suggested the name "clavus helicis." We cannot agree with their concept of the evolution of this condition. In no instance were we able to obtain any evidence of constant daily trauma, which has been found necessary to produce clavus formation on other parts of the body. The location of the nodule also militates against acceptance of it as an ordinary clavus. The majority of the lesions are not located on the uppermost point of the ear, where trauma from above, i. e. from hats, would

most likely produce the necessary daily stimulus for callus formation. Also, one might anticipate a higher incidence in patients wearing glasses and location of the nodule related to contact of the temple bar and the ear if the pathogenesis of the lesion were similar to that of the clavus. The disease was not more frequent, however, in patients wearing glasses, and there was no relationship between the location of the lesion and the temple bar of the glasses. Furthermore, the appearance of the nodules is not that of a clavus. The epidermis over the nodule in the quiescent state is not hypertrophied, nor is there any clinical evidence of hyperkeratosis. On the contrary, the epidermis is likely to be thin, atrophic, and shiny. The epithelium during the acute exacerbation has a variable appearance. It may be thickened and scaly, but more often it is thin and atrophied. Ulceration of the epidermis may be present over the center of the nodule, but there is never a collarette of thickened epithelium, such as is invariably seen in ulcerated clavuses on the feet, for example. We are inclined to interpret the epidermal abnormalities, when present, as a response to and an effect of the pathology seen in the cutis.

Our own concept of the pathogenesis of chondrodermatitis nodularis chronica helicis is as follows: Degenerative tissue and vascular changes which occur in the cutis with advancing age are predisposing factors in the development of the condition. Although this aging process in the cutis is generalized, it is farther advanced on the exposed portions of the body. The relatively thin cutis of the helix is particularly vulnerable because it is stretched tightly over the cartilage. Under these circumstances, minor, often unnoticed, trauma, most likely occurring during sleep, may produce a small focal area of subepidermal injury leading to necrosis. While this might normally heal within a short period of time, in patients with the senile degenerative changes mentioned, repair does not readily ensue and the lesion becomes chronic and persistent. This focal area of necrosis produced in the cutis elicits a response characterized by vascularization, histiocytic proliferation, and an acute or chronic inflammation. The epidermis, in response to the underlying disease process, first hypertrophies and may later become atrophic and ulcerate in the center. The inflammation in the cutis extends downward to involve the perichondrium, with ensuing pain. The cartilage itself is usually not involved except for secondary superficial erosion. The condition has a varied course. The painful nodule may persist, or it may spontaneously subside, although recurrence is the rule.

The accepted method of treatment at present consists of surgical removal of the nodule and a section of the underlying cartilage. Although the immediate results of this procedure may be gratifying, the rate of recurrence is high, as indicated. This consideration, as well as the deforming cosmetic results, led us to inject procaine locally into the lesion in a small series of cases in the hope of averting surgery. Later, procaine and histamine were used in combination, with no clinical evidence of additional curative effect. This method gave results which were as satisfactory as, but no better than, surgical excision. It did, however, avoid the deformity, which was of considerable concern to many patients.

We feel that there is no method of treatment at present which can be depended on to produce consistently satisfactory results. Our present regimen consists of one course of procaine injections, followed by conservative surgical excision if symptoms are not relieved.

SUMMARY

The clinical and pathologic features in 94 instances of chondrodermatitis nodularis chronica helicis are presented against a background of the literature pertaining to the subject. Study of the surgical specimens in these cases indicates that the painful nodule on the helix represents essentially a vascularized organizing inflammatory focus within the cutis. The skin, being relatively thin at this site and tautly stretched over the cartilage of the ear, is vulnerable to minor trauma, particularly when senile degenerative changes and diminished vascularity are present, and by the same token, repair is sluggish, so that recurrence of the condition is commonly observed despite well-conceived treatment. The inflammatory nodule, once established, commonly extends to the perichondrium, but the auricular cartilage itself shows only degenerative changes incidental to aging. These degenerative changes were also observed in a control group of 20 specimens obtained from autopsied subjects of approximately the same age, and, contrary to the prevailing view, they do not appear to play any significant role in initiating the lesion or in its development.

The limitations of the method of treatment employed in the past are pointed out, and a new approach to the problem, utilizing local injection of procaine initially, is suggested.

ACTION OF CORTISONE ON SKIN OF EXPERIMENTAL ANIMALS

Investigations on Protection Against Several Types of Injury to the Skin

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RALEIGH, N. C.

THE CONTEMPORARY literature is replete with reports of the action of adrenocorticotropic and corticoid hormones on various body tissues. The skin has not been exempt from such studies and clinical observations. However, much of the material in this field has been contradictory or inconclusive.

Because of this, the following experiments were undertaken to determine if controlled evidence of a protective mechanism through the use of supplementary corticoid hormone in intact animals could be demonstrated against certain types of injury to the skin. Three rather distinctive and assayable methods of producing alteration in the skin were chosen: (1) ionizing radiation, (2) contact hypersensitivity reaction, and (3) podophyllin (podophyllum resin) damage.

MATERIALS AND METHODS

The cortisone acetate (11-dehydro-17-hydroxycorticosterone; Cortone[1]) used was the commercial preparation and is hereafter referred to simply as cortisone. The injectible form contained 25 mg. per cubic centimeter of solution before further dilution. The ointment form was the commercial ophthalmic preparation containing 1.5% cortisone acetate. In all instances the experimental skin areas were 1 cm. squares. All the histologic specimens were stained with hematoxylin and eosin.[2]

Ionizing Radiation.—The animals used were adult white female guinea pigs averaging 450 gm. in weight. The irradiated areas were clipped on the third day and as frequently thereafter as necessary to observe reactions and properly apply ointment. The radiation factors were 85 kv., 5 ma., through an inherent filtration equivalent to approximately 1 mm. Al, and at 5½ in. (14 cm.) skin-target distance.

Contact-Hypersensitivity Reaction.—The animals used were adult white male guinea pigs averaging 700 gm. in weight. Sensitization was accomplished by applying to a clipped area at the base of the neck five drops of a 2% alcoholic solution of 2, 4-dinitrochlorobenzene daily for seven days. The animals were then rested for 24 days and the elicitating application of a 1% 2, 4-dinitrochlorobenzene solution in olive oil applied to the flanks which had previously been clipped and epilated with calcium thioglycolate cream.

Podophyllin Damage.—The animals used were adult white female guinea pigs averaging 450 gm. in weight. The experimental skin areas were clipped and epilated with calcium thioglycolate cream. Commercial resin of podophyllum, (subsequently designated podophyllin) was employed in all the preparations.

Read at the Seventy-Second Annual Meeting of the American Dermatological Association, Colorado Springs, Colo., April 23, 1952.

1. Much of the cortisone was supplied by Merck & Company, Inc., Rahway, N. J., through the courtesy of Dr. Elmer Alpert.

2. Dr. Thomas B. Wilson reviewed the histologic specimens.

EXPERIMENTAL STUDIES

Ionizing Radiation.—This experiment was devised to determine if local or systemic cortisone would alter the gross or histologic changes which ensue in the skin after exposure to x-radiation. Two animals each received 500, 1,000, and 2,000 r to both sides (exit dose was not measured). Beginning the fourth day after irradiation each of these animals was treated by the irradiated area being anointed on the right side with cortisone ointment and on the left side with petrolatum. This was continued thrice daily for 26 days.

Two guinea pigs subsequently to be treated with parenteral cortisone for observation of the effects of this mode of administration and to serve as controls for possible systemic action of the hormone through absorption from the ointment were subjected to 1,000 and 2,000 r x-radiation to similar areas. These two animals received cortisone intramuscularly beginning 4 days after irradiation and continuing for the succeeding 26 days. For the first eight days 0.25 mg. was given, and subsequently 0.5 mg. twice daily was given. Two animals received 1,000 and 2,000 r x-radiation to 1 cm. squares respectively and no treatment, thus serving as controls.

Table 1 summarizes the observations in regard to dermatitis, epilation, and pigmentary changes at their greatest, presented in the customary grades of + 1 to + 4. Hair regrowth,

TABLE 1.—*Local and Systemic Cortisone and X-Radiation*

G. P. No.	Treatment Begun on 4th Day After Radiation	X-Radiation, R	Degree of Reaction at Height: Dermatitis R.	Dermatitis L.	Epilation R.	Epilation L.	Pigmentary Alteration R.	Pigmentary Alteration L.	Hair Regrowth, 27th Day, % R.	Hair Regrowth, 27th Day, % L.
6	Cortisone ointment t.i.d., r	R. & L.	0	0	++	+	0	0	90	90
		500	0	0	++	++	+	+	75	75
		1,000	+	+	++++	+	0	0	50	50
			+	+++	++++	++++	0	0	25	10
	Petrolatum t.i.d., l	2,000	+++	+++	++++	++++	+	+	0	0
			+++	+++	++++	++++	0	0	0	0
		Right Only								
2	Parenteral cortisone 0.25 mg. b.i.d. 8 days, 0.5 mg. b.i.d. thereafter	1,000	0		++		+		10	
		2,000	++		+++		+		0	
2 (Controls)	None	1,000	0		+++		+		20	
		2,000	++		++++		+		0	

expressed in percentage, was purely an estimation made on the 27th day. Again, there was no appreciable effect from cortisone. It is seen that the degree of reaction paralleled the amount of radiation, and that cortisone used locally or systemically failed to alter these gross changes.

Biopsies of the skin of all the animals were performed on the 18th day folowing irradiation (approximately the height of reaction). In general, the microscopic changes also paralleled the amount of radiation. For the most part, the epidermis exhibited an increase in the granular layer, scattered vacuolation, pyknosis, and karyorrhexis. A few wandering cells, almost entirely mononuclear, were encountered in the epidermis. The corium generally showed a moderate round-cell infiltration, chiefly perivascular. Not only did local and parenteral cortisone fail to exhibit a protective effect against these histologic changes, but in almost all instances when local cortisone was used the changes were greater on the treated side than on the control. There was no appreciable histologic difference between those animals receiving the hormone intramuscularly and the untreated controls.

Contact Hypersensitivity Reaction.—In this experiment 12 male guinea pigs were sensitized to 2, 4-dinitrochlorbenzene. Four were used to determine the effects of locally applied cortisone ointment begun 24 hours after the elicitating exposure to this chemical and continued thrice daily until the dermatitis, which was graded from + 1 to + 4, subsided. Two animals were similarly treated with petrolatum for controls. The first part of Table 2 shows that local cortisone as used here did not reduce the severity nor shorten the course of the eczematous contact-type dermatitis as compared with the controls.

The second part of Table 2 presents the results of parenteral cortisone versus no treatment in the prevention of contact-type eczematous dermatitis in six animals. Cortisone was administered intramuscularly to three of these at the rate of 12.5 mg. daily for two days prior to the elicitating application of 2, 4-dinitrochlobenzene and thereafter until the dermatitis had subsided. The other three animals were untreated controls. With this method of estimating the degree of reaction, no appreciable difference in the two groups in regard to severity or duration could be detected.

No biopsies were performed on skin of the animals under local treatment, but specimens were obtained from each of those receiving parenteral cortisone and their controls. These were taken on the second day after the elicitating exposure to 2, 4-dinitrochlorobenzene. The histologic findings were not striking in either the treated or untreated group, though in the untreated group the animals tended to show a greater and somewhat more acute inflammatory reaction in the cutis. The epidermis was essentially normal in all. The three specimens from animals receiving cortisone showed moderate round-cell infiltration of the corium, while in those from untreated controls these changes were more striking, and, in addition, a scattered polymorphonuclear infiltration was present.

Podophyllin Damage.—In this experiment an attempt was made to determine if local or parenteral cortisone could alter the changes induced in normal skin by the application of podophyllin.

TABLE 2.—*Local and Systemic Cortisone and Contact-Hypersensitivity Reaction*

G. P., No.	Treatment	Degree of Dermatitis Days After Eliciting 2, 4-dinitrochlorobenzene 1	2	3	4	5
4	Cortisone ointment t.i.d. begun 24 hr. after elicitating 2, 4-dinitrochlorobenzene	++++	+++	++	+	0
		++++	+++	++	0	0
		++++	+++	++	0	0
		++++	+++	++	0	0
2 (Controls)	Petrolatum t.i.d.	++++	++	++	+	0
		++++	++	+	0	0
				Biopsy		
3	Parenteral cortisone 12.5 mg. daily begun 48 hr. prior to elicitating 2, 4-dinitrochlorobenzene	+++	++	++	+	0
		+++	++	++	0	0
		++++	+++	++	+	0
3 (Controls)	None	+++	++	++	+	0
		++++	+++	++	+	0
		++++	+++	++	+	0

The results of local application are shown in Chart 1. Areas on the right sides of four guinea pigs were anointed with approximately 40 mg. of 20% podophyllin in cortisone ointment, while, simultaneously, similar areas on the left were anointed with the same amount of 20% podophyllin in petrolatum. Twenty-four hours later and daily thereafter throughout the period of observation the experimental areas on the right were treated thrice daily with cortisone ointment, while those on the left were similarly treated with petrolatum. On the seventh day all reactions were definitely subsiding, and observations were discontinued. The degree of dermatitis was graded from + 1 to + 4 and recorded daily. Chart 1 shows that with this method no appreciable difference between the cortisone-treated right sides and the petrolatum-treated left sides could be demonstrated.

A biopsies of the treated and control areas in all the animals were made on the third day and the specimens examined particularly for "podophyllin effect." In all a moderate connective-tissue proliferation in the corium was present. Some specimens from both cortisone-treated and control skin, presenting severe exudative reactions grossly, were inconclusive microscopically in regard to "podophyllin effect" because of epithelial ulceration and the usual train of inflammatory changes in the epidermis. Epidermal changes consisting of karyorrhexis, distorted mitotic figures, cytoplasmic vacuolation, and pyknosis, which have been so carefully studied by Sullivan and King, were found in a sufficient number of cells to justify interpretation as "podophyllin effect" in only four specimens. These were equally divided between the cortisone-treated and the petrolatum-treated areas. Actually, these changes were somewhat more prominent in skin subjected to cortisone inunction.

Chart 2 presents the experiences with podophyllin skin damage treated with parenteral cortisone. Six animals were employed. Three received 6.0 mg. of cortisone intramuscularly daily, and a like number were not treated. On the third and fifth days of treatment an area on the abdomen of each animal was painted with a solution of 25% podophyllin in 95% alcohol.

LOCAL CORTISONE AND PODOPHYLLIN

NO. OF G.P.	SITE	PODOPHYLLIN EXPOSURE	TREATMENT	DEGREE OF REACTION — DAYS AFTER PODOPHYLLIN						
				1	2	3	4	5	6	7
4	RIGHT SIDE	20% PODOPHYLLIN IN CORTISONE OINTMENT ONCE	CORTISONE OINTMENT t.i.d. BEGINNING FIRST DAY	+	++	BIOPSY ++	++	++	+	
				+	+++	++++	++++	+++	++	
				+	+++	++++	++++	+++	++	
				+	++	+++	DIED			
	LEFT SIDE	20% PODOPHYLLIN IN PETROLATUM ONCE	PETROLATUM t.i.d. BEGINNING FIRST DAY	+	++	++	++	++		
				+	+++	++++	++++	+++	++	
				+	+++	++++	++++	+++	++	
				+	++	+++	DIED			

▨ REACTION DEFINITELY SUBSIDING

Chart 1.

SYSTEMIC CORTISONE AND PODOPHYLLIN

NO. OF G.P.	PODOPHYLLIN EXPOSURE	TREATMENT	DEGREE OF REACTION — DAYS AFTER BEGINNING CORTISONE														
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
3	25% ALCOHOLIC SOLUTION TO ABDOMEN 3rd. AND 5th. DAY AFTER BEGINNING TREATMENT	PARENTERAL CORTISONE 6.0 mgm. DAILY	0	0	0	+	+	+++	++++	++++	++++	++++	BIOPSY ++++	++++	++++	▨	▨
			0	0	0	+	+	+++	++++	+++	+++	+++	+++	+++	+++	▨	▨
			0	0	0	+	+	+++	+++	+++	+++	++	++	++	▨	▨	▨
3		NONE	0	0	0	+	+	+++	+++	+++	+++	+++	+++	+++	+++	+++	▨
			0	0	0	+	+	+++	+++	++++	++++	++++	++++	+++	+++	▨	▨
			0	0	0	+	+	+++	+++	++++	++++	+++	+++	+++	++	▨	▨

APPLICATION OF PODOPHYLLIN

▨ REACTION DEFINITELY SUBSIDING

Chart 2.

The degree of reaction was observed daily and graded from 1+ to 4+. The period of observation was 12 days following the first application of podophyllin, at which time the reaction in all the animals was definitely subsiding. With this method of comparison, the gross changes in the treated and untreated animals were essentially the same as regards severity and duration.

Biopsies were performed on the skin of all animals six days after the second exposure to podophyllin. Inflammatory infiltration and proliferation of connective tissue in the corium were generally present. Changes interpreted as "podophyllin effect" were observed in only two instances, and these were in animals receiving cortisone.

COMMENT

The flood of articles in the recent literature dealing with the adrenocortical hormones would give one pause before essaying a problem of limited scope within this field. However, at the time these experiments were begun there was little published information on the effects of these hormones on cutaneous abnormalities only. Most of the literature concerned scattered clinical observations of cutaneous processes often associated with other organic diseases in which systemic corticotropin (ACTH) and cortisone were used.

For this reason, an investigation of the effects of cortisone on certain types of epithelial changes which are primary in this tissue, not a reflection of disease in other organs, producible in experimental animals and rather consistently reproducible, was considered appropriate. Since the action of cortisone is supposed to be at the mesenchymal level and since consistent changes in both the epidermis and the corium of normal rats under prolonged treatment with topical corticoid steroids had been demonstrated by Castor and Baker,[3] the majority of these studies was concerned with an investigation of the local action of this hormone on the epithelial organ. Three rather distinctive types of injury, namely ionizing radiation, contact-type eczematous reaction, and podophyllin damage, were chosen to test, on the experimental and controllable level, the ability of exogenous cortisone to alter these various types of localized stressful situations in the intact animal.

Ionizing Radiation.—Since the fundamental modes of action on tissue of both ionizing radiation and the corticoid hormones are incompletely understood, it would seem foolhardy to anticipate the outcome of the effects of cortisone on x-radiation changes in normal skin. It did, however, not seem impossible that a hormone with the apparently protein attributes of this one might possibly alter the physicochemical changes induced by ionization of cellular substance. Graham and associates,[4] investigating the protective value of various adrenocortical steroids against the lethal effects of total body irradiation in mice, found little evidence of benefit, although lipoadrenocortical extract given 10 days prior to irradiation protected against 400 r, but not 600 r. However, it seems doubtful that the physiologic mechanisms of irradiation damage and resistance in local and general applications are at all analagous.

It appears that the x-ray doses of 600, 1,000, and 2,000 r used here were within the proper range to produce changes in guinea pig skin varying from slight epilation to marked inflammatory reaction which, from gross observation, were mostly reversible with time.

Though the number of animals is small, the complete lack of evidence of protection from locally applied cortisone in the manner used here would seem indicative of its ineffectiveness (Chart 1). No pertinent literature exists for comparison, except

3. Castor, C. W., and Baker, B. L.: Local Action of Adrenocortical Steroids on Epidermis and Connective Tissue of Skin, Endocrinology **47**:234 (Oct.) 1950.

4. Graham, J. B.; Graham, R. M., and Graffeo, A. J.: The Influence of Adrenal Cortical Hormones on Sensitivity of Mice to Ionizing Radiation, Endocrinology **46**:434 (May) 1950. Graham, J. B., and Graham, R. M.: The Modification of Resistance to Ionizing Radiation by Humoral Agents, Cancer **3**:709 (July) 1950.

possibly the reports of Baker and his co-workers,[5] in which a suppression of hair growth in normal rats was shown to occur after the use of topical corticosteroid hormones. However, the studies reported here are not parallel in regard to animal species, normality of skin, or duration of treatment.

The effect of systemically administered cortisone against this type of damage can not be judged on the basis of two animals, especially since the amount of radiation was rather large (1,000 and 2,000 r). These were included as controls against absorption effects of the locally applied agent. However, there was no appreciable difference between these animals and the untreated controls.

Histologic examination of skin sections at the approximate height of the irradiation reaction corroborated the gross findings, pointing to lack of protective effect of cortisone used locally or systemically. The microscopic changes were in general rather meager in comparison with the gross changes but were consistent with the amount of radiation.

One might conjecture that since a principal effect of cortisone is suppression of inflammatory and proliferative changes, and that since fundamentally ionizing radiation—no matter the magnitude of dose—is destructive, leading to degenerative cellular phenomena, no protective effects could be expected in this type of experiment.

A similar lack of benefit from cortisone against the early effects of x-irradiation of rabbit eyes has also been encountered in another experiment.

Contact-Hypersensitivity Reaction.—The many reports, some with contradictory results, concerning the influence of corticotropin and cortisone on various facets of the cutaneous hypersensitive state, such as tuberculin-type reaction, Shwartzman and Arthus phenomena, drug eruptions, whealing, atopy, and anaphylaxis, will not be dealt with here, since their pathologic physiology is not identical with that of contact-type eczematous reaction.

The literature on cortisone and corticotropin has recently contained references[6] on the efficacy of these hormones in shortening the course and reducing the severity of eczematous contact-type dermatitis in humans. Others have reported less favorable results.[7] Some have found topical cortisone to be of value,[8] while others have

5. Baker, B. L.: The Relationship of the Adrenal, Thyroid, and Pituitary Glands to the Growth of Hair, Ann. New York Acad. Sc. **53**:690 (March) 1951. Ingle, D. J., and Baker, B. L.: The Inhibition of Hair Growth by Estrogens as Related to Adrenal Cortical Function in the Male Rat, Endocrinology **48**:764 (June) 1951. Whitaker, W. L., and Baker, B. L.: A Comparison of the Direct Action of Estrogen and Adrenal Cortical Extracts on Growth of Hair in the Rat, J. Invest. Dermat. **17**:69 (Aug.) 1951.

6. Mote, J. R., editor: Proceedings of the Second Clinical ACTH Conference, New York, Blakiston Company, 1951, Vol. 2, pp. 422 and 424.

7. Mote,[6] p. 423.

8. Spies, T. D., and Stone, R. E.: The Effect of the Local Application of Synthetic Cortisone Acetate on the Lesions of Iritis and Uveitis, of Allergic Dermatitis, and of Psoriasis, South. M. J. **43**:871 (Oct.) 1950. Spies, T. D.; Stone, R. E.; Garcia-Lopez, G.; Milanes, F.; Lopez-Toca, R., and Reboredo, A.: An Appraisal of ACTH and Cortisone as Therapeutic Agents, ibid. **44**:1034 (Nov.) 1951.

had the opposite experience.[9] Recently, Goldman and associates[10] have demonstrated in clinical material a disappointing lack of effectiveness of local cortisone in a variety of dermatoses and failure to suppress patch-test reactions. This is reminiscent of the previous experiences of Sulzberger and his associates,[11] who gave systemic corticotropin to persons with epidermal hypersensitivities, but it is contrary to the findings of a group at Johns Hopkins Hospital which reported suppression of a positive patch-test reaction to atropine with systemic corticotropin.[12] However, Goldman, Preston, and Rockwell[13] found compound F (17-hydroxycorticosterone-21 acetate) locally injected to be effective in suppressing positive reactions to a variety of patch tests, but not those to poison ivy.

At the time these experiments were begun, no reports concerning the corticoid hormones and animal epidermal sensitization had appeared. Recently, the studies of Baldridge and Kligman[14] have shown a singular lack of effectiveness of systemically administered cortisone against contact-type eczematous dermatitis in guinea pigs. In their work, it was shown to be ineffective in blocking, modifying the development of, or ameliorating the course of sensitization reactions to 2,4-dinitrochlorobenzene. However, Nilzen,[15] also employing guinea pigs, observed that systemically administered cortisone produced a delay in the appearance of hypersensitive skin reactions to 2,4-dinitrochlorobenzene and a partial suppression of severity of the reaction. However, he was unable to obtain this effect when the cortisone was applied or injected locally.

Within the limits of this study, the results are in agreement with the findings of Baldridge and Kligman.[14] Their dose of cortisone was considerably smaller than the one employed here. However, that of Nilzen[15] was approximately the same with the parenteral preparation. The observations reported in this paper seem to be at variance with Nilzen's findings, though no comparison in regard to delay in appearance of dermatitis after elicitating 2,4-dinitrochlorobenzene can be made, since frequent early observations such as he made were not done.

Though the number of animals was small, the results were consistent in that neither parenteral nor local cortisone as used was effective in ameliorating the

9. Callaway, J. L.: ACTH and Cortisone: Their Role in Dermatologic Therapy, South. M. J. **45**:63 (Jan.) 1952. Hailey, H.: The Ineffectiveness of Local Cortisone in Eczema in Schoch Letters, Penicillin Research Center, Southwestern Medical Foundation, Dallas, Texas, April, 1951.

10. Goldman, L.; Thompson, R. G., and Trice, E. R.: Cortisone Acetate in Skin Disease, A. M. A. Arch. Dermat. & Syph. **65**:177 (Feb.) 1952.

11. Sulzberger, M. B.; Sauer, G. C.; Herrmann, F.; Baer, R. L., and Milberg, I. L.: Effects of ACTH and Cortisone on Certain Diseases and Physiologic Functions of the Skin, J. Invest. Dermat. **16**:323 (May) 1951. Sulzberger, M. B., and Baer, R. L.: Year Book of Dermatology and Syphilology, Chicago, Year Book Publishers, Inc., 1950, p. 370. Mote,[6] p. 423.

12. Carey, R. A.; Harvey, A. M.; Howard, J. E., and Wagley, P. F.: The Effect of Adrenocorticotropic Hormone (ACTH) and Cortisone on Drug Hypersensitivity Reactions, Bull. Johns Hopkins Hosp. **87**:354 (Nov.) 1950.

13. Goldman, L.; Preston, R., and Rockwell, E.: The Local Effect of 17-Hydroxy-Corticosterone-21-Acetate (Compound F) on the Diagnostic Patch Test Reaction, J. Invest. Dermat. **18**:89 (Feb.) 1952.

14. Baldridge, C. D., and Kligman, A. M.: The Effects of Cortisone on Experimentally Induced Contact Dermatitis, J. Invest. Dermat. **17**:257 (Nov.) 1951.

15. Nilzen, A.: Some Endocrine Aspects of Skin Sensitization and Primary Irritation, J. Invest. Dermat. **18**:7 (Jan.) 1952.

severity or duration of contact-type eczematous dermatitis. In those animals receiving parenteral cortisone there was no evidence of protective effect when the hormone treatment was begun two days before the eliciting exposure to 2,4-dinitrochlorobenzene.

The histologic changes were mild in those animals used for evaluation of systemic cortisone (no biopsy specimens were obtained from the group receiving local therapy). The untreated animals showed a slightly more marked and acute reaction than those receiving cortisone. However, the small number of animals used and the lack of gross difference probably discredits the significance of these findings.

Podophyllin Damage.—At the time this experiment was begun, the literature contained no reference to similar work. Since then Nilzen [15] has shown that cortisone, used systemically but not locally, gives a slight degree of protection against colchicine, a chemical which produces cutaneous changes similar to podophyllin.[16] However, he commented that cortisone apparently is more effective against those irritants which act primarily on the vascular apparatus (e. g., croton oil) than those which affect the epidermis (e. g., cantharides). He explains the effectiveness of cortisone against colchicine on the basis that its action is both epidermal and dermal, and therefore protection is partial.

In the experiments reported here an attempt was made to block the damage resulting from the use of podophyllin with local and parenteral cortisone. In the first instance, this was attempted by incorporating the one application of podophyllin in cortisone ointment and continuing cortisone inunction. In the second, preliminary systemic cortisone was given in liberal amounts before the first application of podophyllin to the skin and continued daily. Though there is no precedent in this situation, it seems that both the frequency of application of cortisone ointment and the parenteral dose should have been adequate to demonstrate its ability. No gross or histologic evidence of its efficacy could be demonstrated in either group when compared with the controls. The fact that "podophyllin effect" was observed more frequently in the cortisone-treated animals than in the controls is probably without significance in view of the small number of animals used.

King and Sullivan [17] have shown that the characteristic action of podophyllin, like colchicine, is a noxious one, inflicting injury on cellular metabolism and reproduction. Thus, these changes are degenerative and not primarily vascular or proliferative. One might anticipate that the corticosteroids would be ineffective against such phenomena. This ineffectiveness against degenerative changes has been emphasized by Woods [18] in his observations on eye disorders.

Animal experiments which are to be reported elsewhere seem to show a protective effect from cortisone against podophyllin damage to the eye. This corroborates the widespread clinical experience of cortisone treatment in patients in whom podophyllin has been implanted accidentally in the eye. The apparent difference in the reactions of the conjunctiva and the skin is unexpected.

16. King, L. S., and Sullivan, M.: The Similarity of the Effect of Podophyllin and Colchicine, and Their Use in the Treatment of Condylomata Acuminata, Science **104**:244 (Sept. 13) 1946.

17. King, L. S., and Sullivan, M.: Effects of Podophyllin and of Colchicine on Normal Skin, on Condyloma Acuminatum, and on Verruca Vulgaris, Arch. Path. **43**:374 (April) 1947. Sullivan, M., and King, L. S.: Effects of Resin of Podophyllum on Normal Skin, Condylomata Acuminata, and Verrucae Vulgares, Arch. Dermat. & Syph. **56**:30 (July) 1947.

18. Woods, A. C.: Cortisone in Interstitial Keratitis, Am. J. Syph. **35**:517 (Nov.) 1951.

General Comment.—The disappointingly negative nature of these experiments challenges a search for an explanation, especially when, as in the case of contact-type eczematous reaction, it is at variance with considerable clinical experience.

In the first place, the small number of animals employed may have vitiated the results. Species specificity might conceivably contribute to the results. The time of administration of cortisone may well have influenced the outcome. It is possible that an adequate preliminary dose may have produced different results in some of the experiments. The question of proper dose is pertinent, especially with the parenteral preparation. Some experiences seem to demonstrate that for certain effects of the corticoid hormones, the human weight-dose ratio is inadequate when applied to smaller animals. Since the studies concerning local cortisone employed only the ointment form, one might question the amount of cutaneous absorption from this type of vehicle. The demonstration of Baker and his associates that cortisone used locally could produce epidermal atrophy and suppression of hair growth is not quite analagous, since they employed more concentrated preparations, different vehicles, and longer periods of application.

The disparity between these animal experiments, those reported by others, and clinical experiences, especially those concerning the contact-hypersensitive state and podophyllin injury, suggests that further and more varied studies along the same lines are indicated.

SUMMARY

Locally applied cortisone ointment following x-irradiation of guinea pig skin failed to block gross and histologic changes as compared with controls. Parenteral cortisone used in a few animals was likewise ineffective.

Cortisone ointment applied after the eliciting exposure of 2,4-dinitrochlorobenzene in sensitized guinea pigs failed to alter the course of the contact-type eczematous dermatitis.

Parenteral cortisone administered before and after the eliciting exposure of 2,4-dinitrochlorobenzene in sensitized guinea pigs did not affect the clinical course of the dermatitis or significantly influence the histologic picture.

The gross and histologic (including "podophyllin effect") changes occurring after the application of podophyllin to the skin of guinea pigs were not significantly altered by cortisone ointment applied simultaneously and afterward or by systemic cortisone administered before and after the chemical injury.

Possible explanations for this lack of effectiveness are explored and the pertinent literature compared.

ABSTRACT OF DISCUSSION

DR. MARION B. SULZBERGER, New York: Dr. Hitch's presentation is an excellent summary of careful experimental work well evaluated. Although his series is small, I think that the results are probably to be given additional weight because they fit in so very well with the previous clinical observations.

First of all, I think that one can say that cortisone acetate ointment is of no general value in treating skin diseases (except perhaps those around the eyes and orifices). With the above exceptions, my colleagues and I found it of no benefit in topical application in any of the dermatoses in which we have tried it, and these negative results correspond with Dr. Hitch's results. It was of interest to me to try to calculate just what Dr. Hitch was giving translated into the human dose. On the basis of weight were the doses in his animals larger, the same as, or smaller than those given to man? In his irradiation experiment Dr. Hitch used guinea pigs weighing 450 gm., and they got 1 mg. daily. They thus received a little over 2 mg. per kilogram, which would make about 150 mg. a day for an average man.

In the contact-dermatitis experiments, the guinea pigs weighed about 700 gm. each. Each guinea pig got 50 mg. per day, or about 70 mg. per kilogram, making about 4,900 mg. for an average man—which is, of course, a huge dose.

Concerning the guinea pigs that were treated with podophyllin, they received 12 mg. per kilogram, or an average equivalent of 740 mg. for a 70 kg. man.

I should like to call attention to one finding which I think perhaps Dr. Hitch might like to emphasize more after he has heard my discussion. That is the histological difference in the response to 2,4-dinitrochlorobenzene which he found in the animals receiving cortisone systemically. The animals receiving cortisone had less infiltration than the control animals not receiving cortisone in any form.

Now, I should like to sketch only briefly the results my colleagues and I obtained in patch-test reactions to contact allergens in man and also some of our clinical experiences with cortisone used locally and systemically to show how well they correspond with Hitch's findings.

First of all, this hormone is rapidly effective against human contact-type dermatitis when given systemically. Cortisone in adequate dose given systemically removes the signs and symptoms of the disease temporarily, i. e., it has a rapid "morbidistatic" effect. Contrariwise, we have found cortisone entirely ineffective in this same group of diseases when applied locally. It was also ineffective in controlling the experimental dermatitis when applied after the application of patch tests with contact allergens. Cortisone was also ineffective when given systemically before, during, and after patch tests when applied in man, provided we used only the standard concentrations of the patch-test materials. But as soon as we did serial dilutions of our patch-test materials and gave cortisone systemically before and during the application of the skin tests, we found a discernible quantitative reduction in the response. In other words, when we got to or near the end-point of dilution, the patients being given cortisone gave less reactions than the same patients had given while not on cortisone. There was a quantitative change, a raising of threshold, produced by the systemic administration of cortisone. I think that the equivalent of this result in man may be reflected in the less histologic response of the animals being given systemic cortisone which Dr. Hitch obtained when he tested them with 2,4-dinitrochlorobenzene. This effect, the effect of systemic administration of cortisone in reducing the skin sensitivity somewhat, was demonstrated by us in patients with sensitivities to various different eczematogenic allergens (e. g. to procaine hydrochloride, to paraphenylenediamine, and to iodochlorhydroxyquin [Vioform]).

It is interesting to speculate why the local application of cortisone should be so often effective in the eye (and around the eye) and ineffective on the skin generally. Is it a difference in penetration? Probably not, because cortisone is found to be ineffective when applied locally even on denuded areas of the skin and even when injected intracutaneously. It seems more probable to me (and I shall not be able now to give you all the supporting data for this belief) either that there are absent in the skin and present in the eye activators which change cortisone into something locally effective, or that there are present in the skin and absent in the eye cortisone-inactivators which inhibit the local beneficial effects. I am inclined to lean somewhat toward the first hypothesis.

If either of these hypotheses is correct, it is possible that the local application of compound F may prove effective in some of those skin diseases in which the systemic administration of cortisone is effective.

DR. JOSEPH M. HITCH: I want to thank Dr. Sulzberger for his discussion. His comparison of clinical experiences which he and his group have observed with the animal experiments presented here is enlightening.

There is no single explanation for the variable dose of cortisone, except lack of precedent. However, in the experiments dealing with irradiation, a small dose was chosen in anticipation of long-continued treatment.

Dr. Sulzberger called attention to the fact that in the 2,4-dinitrochlorobenzene sensitization experiments the cortisone-treated animals showed somewhat less histologic changes than did the controls. This finding was not emphasized because I felt that the small number of animals and the slight pathologic differences made the observation inconsequential. In the light of Dr. Sulzberger's dilution-patch-test experiences one must entertain the idea that perhaps the animal observations have significance.

DERMATITIS OF THE HANDS

Etiology and Principles of Treatment, with Observations Concerning a Hyperkeratotic Dermatitis of the Volar Skin

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A SCHOLARLY and authoritative treatise, "Infections of the Hands," by Kanavel,[1] devotes over 500 pages to monographic exposition of this subspecialty of surgery. "Dermatitis of the Hands" is a subject of equal rank, a subspecialty of dermatology worthy of monographic studies as yet unwritten, a book-size title, and we can here only outline what such a book might contain. We can present some useful and practical ideas for the interpretation and management of conditions which give rise to an immense amount of suffering and which constitute some 9%[2] of the daily medical endeavor of a practicing dermatologist. The usual patient is a young matron,[3] who must keep house, cook, wash dishes, do the laundry, raise her children, and hold her husband; who can ill afford to sustain the misery of manual disability, and whose occupation is inherently one of the most hazardous with which the dermatologist commonly has to deal.

Read at the Seventy-Second Annual Meeting of the American Dermatological Association, Colorado Springs, Colo., April 23, 1952.

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1. Kanavel, A. B.: Infections of the Hand: A Guide to the Surgical Treatment of Acute and Chronic Suppurative Processes in the Fingers, Hand and Forearm, ed. 6, Philadelphia, Lea & Febiger, 1933.

2. Lane, C. G.; Rockwood, E. M.; Sawyer, C. S., and Blank, I. H.: Dermatoses of the Hands, J. A. M. A. **128**:987-992 (Aug. 4) 1945. The authors review the literature and report on 475 cases of eczema of the hands. Most were instances of bacterial, not mycotic infection. (See footnotes *32* and *33 b* and *c*.) These authors report that fungus cultures are not worth while and that patch tests are not of real value. In order of frequency, the diagnoses were infectious eczematoid dermatitis, dermatophytid, bacterid, psoriasis, atopic dermatitis, pompholyx, dietary insufficiency, and tinea. "Nummular eczema" is not an entity but is merely descriptive. Cases often start with mechanical or chemical trauma in a vasomotor-susceptible person who has elsewhere in the body an infection which alters the relation of the host with the normal resident flora. Treatment involves avoidance of contactants; use of boric acid compresses, zinc oxide paste, sulfonamides, and staphylococcus toxoid and elimination of focal infection.

3. Jordan, J. W.; Dolce, F. A., and Osborne, E. D.: Dermatitis of the Hands in Housewives, J. A. M. A. **115**:1001-1004 (Sept. 21) 1940.

If one should write a book on dermatitis of the hands, the table of contents of the Suttons' "Handbook of Diseases of the Skin," [4] with its etiologic classification, would require little change to fit it. General considerations of anatomy, embryology, physiology, symptomatology, pathology, etiology, diagnosis, and treatment would comprise the introduction. This would be followed by essays on dermatoses due to physical agents, chemical agents, and parasites of the various sorts; dermatoses representative of disordered metabolism, vascular function, neurologic and psychic function, atrophy, and pigmentation, and growth disorders of malformation and neoplasia. Finally, there would be a necessarily thick chapter devoted to disorders of as yet undetermined cause.

PERTINENT CUTANEOUS ANATOMY

The skin as a whole is the dividing line between the person and his environment. It combines the features of a barrier, an adaptive mechanism, and a sensory organ—a great deal is asked of it, so to speak. It is composed, in effect, of two layers, the epidermis and the dermis. Its keratin coating is relatively inert, impervious to water, and resistant to acids. It is less resistant to alkali, under the influence of which the cell bodies swell and loosen from one another.

When there is loss only of epidermis, new epithelial cells are reproduced by those which remain at the edges of or beneath the area of loss, and there soon will be *restitutio ad integrum* if nothing interferes with the process of healing. When dermal tissues are lost, on the other hand, proliferation of fibrous and granulation tissue is necessitated, so that healing requires the construction and maturation of scar tissue. Thus a simple epidermal damage heals in a few days, approximately a week, without lasting alteration, if its causes cease to function, while dermal loss requires a longer time to heal and produces scar. Dermal inflammatory infiltrates may or may not be completely reversible.

The skin of the hands anatomically is characterized by a sparseness of tissue that skin elsewhere does not manifest. There is no skin to waste on hands. The dermis is dense and comparatively avascular. A circular skin defect, full thickness, of 1 cm. diameter, which would granulate and heal on the face in 26 days, requires 40 days to heal if located on the dorsum of the hand. Reversible dermal inflammatory infiltrates do not have, in the skin of the hands, the richness of vascularity which abets the healing of dermatitis located elsewhere.

The volar epidermis, which extends over the sides of the fingers, comprises a large proportion of the total epidermal tissue of the hands and is extremely thick. It is richly supplied with sweat glands, but hair and sebaceous glands are absent. The sweat ducts are tiny; they coil their way through the thick epidermis and are vulnerably fragile. A loss of volar epidermis requires longer to heal than a loss of similar area in a location where the epidermis is thinner. When epidermis is damaged and epithelial cells swell and burst, some by-products of dead epidermis must be absorbed. When volar epidermis is the site of such a process, there is a great quantity, relatively, of altered epidermal material available for absorption, and it would seem that the absorption of it results in damage of a toxic sort to

4. Sutton, R. L., and Sutton, R. L., Jr.: Handbook of Diseases of the Skin, St. Louis, C. V. Mosby Company, 1949.

epithelium distantly located, for vesiculating disease of the soles induces vesiculation of the palms, and vice versa. The autoeczematization phenomenon, as elucidated by Cormia and Esplin,[5] may so come into play.

PERTINENT CUTANEOUS PHYSIOLOGY

Physiologically, the skin as a protective mechanism, in addition to its physical properties, supports a constant flora of nonpathogenic organisms and is liable to the influx of pathogens. If the skin is dry and cool, pathogens cannot thrive, and drying is one of the mechanisms of self-sterilization.[6] The impossibility of attaining a state of coolness and dryness of the skin explained the impossibility in the tropics of curing the coccic infections which caused many casualties in World War II. Patients with "jungle rot" when returned to the Zone of the Interior for the most part got well rather promptly. Although many of them were returned with a diagnosis of fungous infection, one of us (R. L. S., Jr.) recovered on cultural studies few parasites other than hemolytic Micrococcus aureus and streptococci. The skin also gets rid of things by exfoliation.[6] Greasy applications may interfere with this function.

The hands have less latitude in accommodating themselves to environmental temperatures than other parts because they are not massive and because they offer a large surface, per unit of weight, of exposure to their surroundings. Their skin is frostbitten, sunburned, and macerated in a manner to which skin located elsewhere is not subjected.

As an organ of sensation, the skin is of great significance, for it mediates the psyche with the physical world by means of tactile, pain, and temperature sensibility, and the hands embody the principal and most highly developed sensibility of any part of the skin. The eyes mediate perception of electromagnetic energy, the ears respond to vibrations of the atmosphere, and the hands mediate perception of the material features of the external world by physical contact. As microscopic matter concerns the sense of smell, so megascopic matter concerns the sense of touch.

Psychosomatic influences[7] and relationships are therefore highly significant in some cases of dermatitis of the hands. The hands are busy if the mind is busy. The hands are agitated if the mind is agitated. The hands are the organs of doing things with things. They pick at, pry at, rub, and investigate, and they do these things not only to external objects but to themselves. The patient with dermatitis of the hands is much tempted to move, flex, and extend his fingers, to test the sensibility of his hands, and to keep inflamed tissues continually in motion, and if he is worried he does it the more. The patient with dermatitis of the hands has to be exhorted to keep his inflamed skin at peace. Sweating is in part controlled

5. Cormia, F. E., and Esplin, B. M.: Autoeczematization: Preliminary Report, Arch. Dermat. & Syph. **61**:931-945 (June) 1950.

6. Burtenshaw, J. M. L.: Self-Disinfection of Skin: Short Review and Some Original Observations, Brit. M. Bull. **3**:161-164, 1945.

7. Stokes, J. H.; Lee, W. E., and Johnson, H. M.: Contact, Contact-Infective and Infective-Allergic Dermatitis of the Hands, with Special Reference to Rubber Glove Dermatitis, J. A. M. A. **123**:195-202 (Sept. 25) 1943.

by sympathetic nervous influences, and the tense and anxious person has cool, wet palms. Sometimes the volar skin actually drips perspiration. Such persons are more than normally susceptible to maceration and to bacterial and fungous infections and are subject to recurrent and recalcitrant attacks of fine vesiculation, pompholyx so-called, and secondary infection thereof.

MECHANISMS PROVOKING DERMATITIS

Inflammation is a vascular activity,[8] not fundamentally different in skin than in other organs. Damage by any mechanism first results in outpouring of lymph, followed by the clotting thereof, and the intratissue clot acts as a mechanism of fixation. Bacteria caught in the web cannot move about rapidly, and the clot acts as a filter and picks out of the circulation whatever foreign substance may be present. Immunity is a function of inflammation, and allergy is a variant of immunity representing, in the broad outlook, a failure of successful immunity, being a specifically altered reactivity to exposures to specific noxae subsequent to the sensitizing exposure. Contactant allergy is an extremely important factor in skin diseases in general, and because of the function of the hands as organs of touching and doing, their skin is subject, more than skin located elsewhere, to the development of contactant sensitivity. Contactant disease in general may be divided into (*a*) primary irritation provoked by chemicals irritating any normal skin, and the hands get into these, and (*b*) sensitization by chemicals which affect different individuals differently because of the development of allergy, and the skin of the hands, more than other skin, gets into these.

The skin of the hands is exposed to the potentiality of diseases provoked by heat, cold, light, moisture, irritant chemicals, sensitizing chemicals, and pathogenic organisms to a degree over and above other skin. It is subject additionally to all the diseases of internal origin that skin is elsewhere, and the hands are especially subject, being special tactile organs, to psychosomatic disturbances.

The mechanisms provoking inflammatory skin disease of the hands are at least 10 in variety:

1. Trauma of all kinds, including friction and excoriation.

2. Contactant injury by primary irritants, which provoke changes like those induced by trauma and which heal similarly.

3. Contactant injury by senstizers, which alter the reactivity of the skin more or less permanently, so as to provoke itching, redness, and vesiculation when the skin is touched even in minute concentration.

4. The mechanisms of injury by chemical substances absorbed and provocative of intoxication, of allergic reactions such as dermatitis medicamentosa, including fixed eruptions, or of food allergy.

5. The mechanisms of locally invasive parasites, including viruses, bacteria, and fungi as well as animals such as Acarus scabiei.

6. The mechanism of focal infection, which influences the distant site perhaps by supplying circulating parasites or by-products of parasites to be filtered out by an already-existing inflammatory reaction, or perhaps by supplying parasites which reach the skin via its surface, so that the flora continually contains pathogens.

7. The mechanisms of nervous and mental, or psychiatric, abnormality, including anxiety, excoriation, and self-mutilation.

8. The mechanisms of cutaneous changes due to nutritional deficiencies, metabolic defects, and hormonal imbalances.

8. Sutton and Sutton,[4] p. 26.

9. "Lowered resistance"[9] of the individual, rendering the skin susceptible to inflammation or infection. While this is ill understood and may be pertinent to heredity ("diathesis"), psyche, nutrition, or foci of infection, it is evidently a reality which teases a mind that seeks explanations, and it demands some sort of recognition.

10. Combinations of these mechanisms.

ETIOLOGIC CLASSIFICATION OF DERMATITIS OF THE HANDS

PHYSICAL AGENTS.—Trauma, friction, heat, cold, moisture and maceration, and radiation (actinic, roentgen, or radium) may be listed. Etiologic diagnoses, respectively, would include, for example, cuts, bruises, crushing injuries, chapping, burns, frostbites, sunburn, and roentgen ray dermatitis and atrophy. Treatment for such dermatitides must include elimination of further action of the noxious agency, appropriate alterations of environment of the hands, and palliative protection while the skin is allowed to heal as well as it can. Restorative efforts appropriate to some cases might even include plastic surgery.

The defatting and drying effects of soap and the detergents, as in washing dishes, especially during cold weather, frequently initiate an eczematous eruption of the hands, which may be further aggravated by any one of many common household irritants, such as bleaches, waxes, polishes, and, often enough, hand lotions and cold creams. Secondary infection, especially with micrococci, is likely to follow.

CHEMICAL AGENTS.—*External Chemical Injuries.*—These include the effects of primary irritants and of sensitizers. The etiologic diagnosis is dermatitis venenata. Treatment requires elimination of contact with injurious chemicals, palliation of symptoms, and prevention of secondary infection while the skin heals.

The differential diagnosis between contact dermatitis and dermatitis of the hands from internal causes is not always easy. In general, contact dermatitis is more likely to involve the backs of the hands, the backs and sides of the fingers, and the interdigital webs, whereas eruptions of internal origin are more frequent on the palmer surfaces. Exceptions, however, are provided by substances to which the hands are sensitive and which are grasped, such as nickel, rubber or plastic handles, rubber hose, and kitchen-knife handles.

A common history is that of an eruption beginning on the left fourth finger under rings and later spreading to other portions of the hands. This eruption is evidently initiated by the retention of dish-washing soaps or detergents beneath the rings as the result of inadequate rinsing. Then the injured skin is invaded by bacteria, usually Micrococcus aureus, which maintain the disease even if irritating chemicals are avoided.

"Id" Reactions.—So-called "id" reactions may produce eczematous eruptions of the hands. The "id" reaction is probably a type of allergic response and is most commonly seen on the hands after an acute dermatophytosis of the feet, but a microorganism is not necessary for the production of an "id" reaction. A severe chemical dermatitis of the feet may produce an "id" eruption of the palms, and vice versa.

Keratolysis Exfoliativa.—The lesions are small, rounded, peripherally expanding, shallow, scaling macules affecting volar skin, initiated by tiny, tender or itchy, presumably vesicular puncta occurring in crops. While it is possible that in some

9. Barber, H. W.: Acrodermatitis Continua vel Perstans (Dermatitis Repens) and Psoriasis Pustulosa, Brit. J. Dermat. **42**:500-518 (Nov.) 1930.

instances this condition represents dermatitis venenata, there is general agreement with MacKee and Lewis [10] that it is usually a dermatophytid. It has been known to depend upon fungous infection of the vagina [11] as well as of the feet.

Dermatitis of Internal Origin.—This may be caused by hypersensitivity to chemical substances ingested, inhaled, or injected; by allergenic foods or nutritional deficiencies in vitamins or protein; by endocrine disorders of oversupply, imbalance, or deficiency, and by metabolic chemical errors. Exemplary etiologic diagnoses of such dermatitides include dermatitis medicamentosa, allergic eczema due to foods,[12] urticaria, pellagra, keratoderma climactericum,[13] myxedema, diabetic gangrene, and xanthoma. Treatment for such diseases requires elimination of allergens, adequate replacement of such necessary drugs or foods as must be eliminated, addition of adequate vitamins or other nutrients, and correction of endocrine imbalance or metabolic error so far as this can be achieved, along with palliation and prevention of complications.

Food Allergy.—This is perhaps a factor in a small percentage of cases of dermatitis of the hands. Winston and Sutton [14] thought that they identified food allergens as causative of dermatitis with fairly characteristic features. The eruptions are persistent, with flares. They are located on the dorsums of the hands and about the wrists. They are dry, nonvesicular, and lichenoid and are roughly circular. The typical feature is the presence of gouged-out excoriations, which are made by the patient during his sleep, for he can refrain from digging his hands when he is conscious. Winston was not able to confirm the belief of Flood and Perry [15] that food intolerance can evoke vesicular eczema. Identification of causative foods was accomplished, not by scratch tests or elimination dieting, but by the single-food additive diet. In this the patient eats one food during 24 hours, after which the hands are examined for the presence or absence of telltale excoriations. If these are absent, the food is adjudged innocuous and another food is added to the allowance of ingesta. When a food is added and is followed by itching and gouging, it is judged probably injurious and is omitted from the diet for some time; later it is retested. Thus one proves, after careful observation, which foods are harmful and which are harmless.

Nutrition.—Vitamin deficiencies provocative of dermatitis of the hands are typified by pellagra. There are, however, occasional unrecognized cases of vitamin

10. MacKee, G. M., and Lewis, G. M.: Keratolysis Exfoliativa and the Mosaic Fungus, Arch. Dermat. & Syph. **23**:445-471 (March) 1931.

11. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 10, St. Louis, C. V. Mosby Company, 1939, p. 1032.

12. Livingood, C. S., and Pillsbury, D. M.: Specific Sensitivity to Foods as a Factor in Various Types of Eczematous Dermatitis, Arch. Dermat. & Syph. **60**:1090-1115 (Dec.) 1949.

13. Haxthausen, H.: Keratoderma Climactericum, Brit. J. Dermat. **46**:161-167 (April) 1934.

14: Winston, B. H., and Sutton, R. L., Jr.: Dermatitis of the Hands Due to Ingested Allergens, Arch. Dermat. & Syph. **58**:335-348 (Sept.) 1948.

15. Flood, J. M., and Perry, D. J.: Recurrent Vesicular Eruptions of the Hands Due to Food Allergy, J. Invest. Dermat. **7**:309-327 (Dec.) 1946; Role of Food Allergy in Eczematoid Dermatitis, Arch. Dermat. & Syph. **55**:493-506 (April) 1947.

B deficiency, sometimes associated with macrocytic nutritional anemia,[16] in which eczematous dermatitis of various types suggests pellagra. It is difficult to recall any such cases in which the hands were exclusively involved, although cases have been observed in which the hands were involved along with other parts of the body. Vitamins other than the B complex are seldom critically concerned with dermatitis, we believe, although Gross[17] would associate nummular eczema, its winter exacerbations, and asteatosis with the need for vitamin A, which he gave to 24 patients with benefit to 18 of them.

The relationship of protein nutrition to chronic lichenoid eczematoid dermatitis is important, as the Guys and their collaborators[18] have emphasized. In many a patient with such dermatitis, one of us (R. L. S., Jr.) has found the total serum protein ranging from about 5.6 gm. per 100 cc. to 6.4 gm., and the patient has improved on a diet high in protein and injections of vitamin B_{12}.

Impaired liver function is often associated with a disturbed protein nutrition. A number of instances of hyperkeratotic dermatitis of the palms as well as other dermatoses, including scattered localized neurodermatitis, nondescript eczematous eruptions, and severe flexural dermatitis, have been encountered during the past several years in which an impaired liver function was revealed by the sulfobromophthalein (Bromsulphalein) test.[19] The condition usually responded satisfactorily to a program of a low-fat, high-protein, adequate-carbohydrate diet, abstinence from alcohol, intramuscular administration of a crude liver extract containing folic acid in a dose of 2 cc. (2 I. U. per cubic centimeter) once a week, use of a high-potency vitamin B complex, and oral administration of a lipotropic substance (Methischol, which contains *dl*-methionine, choline, and inositol, together with the natural B complex from liver).

The following case is relevant.

A. B., a white man aged 36 years, a postal clerk, in March, 1949, exhibited patches of chronic lichenoid dermatitis of the legs which were of one year's duration, with similar lesions of the fingers and dorsums of the hands and wrists of more recent onset. He was at first instructed in the avoidance of the most likely contactant irritants and in the use of cool aluminum acetate compresses and zinc oxide paste. Later several doses of x-ray therapy of 75 r at 100 kvp, no filter added, were administered. His dermatitis remained variable and recalcitrant. There were episodes of flares, exudation, and extension of the lesions and partial subsidences. Topical therapy was altered from time to time, with use of potassium permanganate soaks, bacitracin ointment, iodochlorhydroxyquin (Vioform) cream, one-third strength benzoic and salicylic acid ointment with 3% sulfur added to it, 1% coal tar ointment, aureomycin ointment, silver nitrate applications and soaks, and so forth. Search for focal infection revealed pus in the prostatic fluid, and the prostate was thereafter methodically massaged, and sulfonamides were given orally. Vitamin therapy was pushed. X-ray treat-

16. Stryker, G. V., and Halbeisen, W. A.: Determination of Macrocytic Anemia as an Aid in Diagnosis of Certain Deficiency Dermatoses, Arch. Dermat. & Syph. **51**:116-123 (Feb.) 1945.

17. Gross, P.: Nummular Eczema: Its Clinical Picture and Successful Therapy, Arch. Dermat & Syph. **44**:1060-1077 (Dec.) 1941.

18. Guy, W. H.; Jacob, F. M., and Guy, W. B.: Geriatric Nutritional Eczema, Arch. Dermat. & Syph. **57**:822-827 (May) 1948. Guy, W. B.: Protein Deficiency in Cutaneous Disease, ibid. **61**:261-270 (Feb.) 1950.

19. Ayres, S., Jr.; Ayres, S., III, and Mirovich, J. L.: Macrocytic Anemia and Impaired Liver Function in Eczematous and Certain Other Dermatoses, Arch. Dermat. & Syph. **62**:851-869 (Dec.) 1950.

ment was pursued until the cumulative dose in a period of 15 months reached 1,400 r in some areas, for its use was generally followed by temporary improvement. When severe dermatitis followed the patient's application of thimerosal (Merthiolate) to his fingers, there was a period of optimism regarding the likely benefit of pushing yet further the program of controlling contactants. This program proved unavailing, although the patient was shown by patch test to be intolerant to mercurials. Not until June, 1950, was protein nutrition investigated.

It had been the patient's habit to eat meat only three or four times a week. Within one week of a high-protein diet, improvement was conspicuous. Within three weeks his hands were better than they had been at any time since the onset of dermatitis and were no longer itchy. After six weeks of a high-protein diet, there was no dermatitis left, although he discontinued concern with contactants and pursued unvaried his occupation and normal way of life. Adequate protein nutrition cured this man's dermatitis.

PARASITISM.—*Infections from the Exterior.*—These may be caused by viruses, rickettsiae, bacteria, fungi, protozoa, or metazoa. Exemplary etiologic diagnoses include warts, molluscum contagiosum, and milker's nodes; rickettsial pox; micrococcic or streptococcic impetigo, or a mixed form, infectious eczematoid dermatitis, furuncle carbuncle, diphtheria cutis, anthrax, even primary tuberculosis of the skin, and syphilis; dermatomycoses due to specific fungi, such as Trichophyton mentagrophytes; oriental sore and amebiasis cutis, and metazoan parasitic diseases ranging from schistosomal swimmers' itch through myiasis, scabies, and tick bites.

Superficial fungous infection of the hands is relatively rare in spite of the frequency with which this diagnosis is made. The diagnosis should be made only after the organism is demonstrated by direct potassium hydroxide mounts examined microscopically or by culture on Sabouraud's medium. The commonest fungus affecting the hands in the western part of the United States is Trichophyton purpureum (rubrum), and it usually attacks both feet and only one hand, frequently also involving the nails. The eruption is ordinarily inconspicuous, consisting of fine, dry scaling with slight erythema, usually affecting the palm but sometimes extending to the dorsal aspect. It is indeed recalcitrant to treatment. Yeast-like fungi, usually Candida (Monilia) albicans, occasionally attack one or more interdigital webs, producing a red, glazed appearance with slight peripheral scaling, and they also may cause chronic paronychia, especially in persons whose hands are wet much of the time.

Therapy appropriate to parasitism may be made highly specific, topically or systemically, in an effort to make life hard for the parasite and easier for the host. Identification of parasites is essential to optimal treatment, smears, cultures, dark-field examination, serologic and immunologic tests, tests for antibiotic sensitivity, and animal inoculations being utilized. Few parasites nowadays are resistant to every known antiparasitic chemical substance. Cool, dry, illuminated skin does not support flora as does warm, moist skin in the dark. Débridement is as necessary in tinea pedis as in military surgery, and what is roentgen epilation but a special form of débridement?

If all the influences adverse to healing, including parasites, can be sufficiently impeded and when sufficient time has elapsed, the patient gets well. A patient heals himself if circumstances are favorable and if he has the capacity. He cannot be forced to get well.

Infections from the Interior Comprising Focal Infections.—Significant foci may exist in teeth, gums, tonsils,[20] sinuses, prostate,[21] cervix, bladder, gastrointestinal tract,[20e] and even distant sites of skin disease. Focal infection [22] is simple to comprehend biologically. We shall define it as a commonly occurring host-parasite relationship wherein pathogenic organisms are located in the host in a circumscribed lesion, from which they can be eliminated only by the performance of a mechanical alteration, such as an extraction, excision, or plastic repair. Such parasitism persisting locally makes pathogens and their by-products constantly available for their possible influence upon, or invasion of, other tissues of the host when opportunity offers. In pyorrhea, streptococci and staphylococci are present and ready to infect the skin once it is damaged by, let us say, contact dermatitis. In cystocele with residual urine and chronic cystitis, bacteria are ever-present.

Focal infections provide for the continual presence of transient pathogens among the skin flora; for, when any part of the body is infected with streptococci, pathogens are plentiful on healthy skin areas.[23] Not only may foci of infection feed pathogenic bacteria into the circulation and finally into damaged skin, but such foci perhaps may also lead to sensitization of tissues elsewhere, so that the products of bacterial growth in the foci may enter the circulation and upon reaching previously sensitized tissues result in various pathological entities, as, for example, chronic urticaria. Diagnoses exemplary of dermatitis due to focal infection include recalcitrant pustular acrodermatitis,[24] and, in many cases, simply chronic dermatitis of the hands.[25] The treatment of such conditions requires adequate search for and elimination of foci, and the dermatologist welcomes especially the assistance of competent dental, genitourinary, and gynecologic consultants. The elimination of foci by extractions, oral hygiene, tonsillectomy, pelvic repair, cauterization of the cervix, prostatic massage, or even diligent dermatologic attention to pedal dermatomycosis, onychomycosis, or seborrheic dermatitis of the scalp (which may indeed serve as a chronic source of failure to cure dermatitis

20. (*a*) Barber, H. W.: Pustular Psoriasis of the Extremities (4 Cases Discussed Nov. 17, 1932, Before the Royal Society of Medicine, Section on Dermatology), Proc. Roy. Soc. Med. **26**:329-333 (Feb.) 1933. (*b*) Andrews, G. C.; Birkman, F. W., and Kelly, R. J.: Recalcitrant Pustular Eruptions of Palms and Soles, Arch. Dermat. & Syph. **29**:548-563 (April) 1934. (*c*) Andrews, G. C., and Machacek, G. F.: Pustular Bacterids of the Hands and Feet, ibid. **32**:837-847 (Dec.) 1935. The authors reported that tonsils and teeth, especially, served as foci, as also might duodenal ulcer, chronic colitis, and arthritis. Cases in which there are such foci constitute the single group, among all cases of pustular eruption, in which elimination of focal infection affords the only cure. (*d*) Andrews, G. C., and Barnes, M. C.: Pustular Bacterids and Allied Conditions, South. M. J. **34**:1260-1266 (Dec.) 1941.

21. Carpenter, C. C.; Nuckolls, C. R., and Dyke, J. S.: Nummular Eczema and Prostatitis: Its Treatment with Penicillin, U. S. Nav. M. Bull. **47**:453-457 (May-June) 1947.

22. Sutton, and Sutton:[4] Focal Infections in Etiology of Dermatoses, p. 36; in Infectious Eczematoid Dermatitis, p. 164; in Rosacea, p. 399; in Acne, p. 407; in Chronic Dermatitis, p. 489; in Psoriasis, p. 522; in Discoid Lupus Erythematosus, p. 532; in Sycosis Barbae, p. 675.

23. Martin, N. H.: Pyogenic Skin Infections and the Skin-Carrier Rate, Brit. M. J. **2**:245, 1942; cited by Sutton and Sutton,[4] p. 171.

24. Steiner, K.: Acute Recurrent Pustular Bacterid, Arch. Dermat. & Syph. **58**:220-223 (Aug.) 1948. (The author confirms the findings of Andrews and associates.[20 b, c, d])

25. Sutton, R. L., Jr.: Dermatitis of the Hands, J. Missouri M. A. **46**:410-413 (June) 1949.

elsewhere [26]—such elimination of parasitism limited to small regions, but deleteriously influential upon distant areas, makes sense in theory and succeeds in practice. The following cases are typical.

Mrs. A., 26 years of age, with two small children to tend, a household to run, the dishes to wash, and the laundry to get out in the time not devoted to her sewing and church circles, complained that her hands had been sore most of the time for two years. Her physician tried to get her away from contact with strong cleansing agents, which are the usual cause of dermatitis of the hands in the housewife. He pursued his investigations with diligence and science, discovering that she had a positive patch-test reaction to a certain washing powder. Changing detergents, however, did not bring about a cure. He learned that the trouble began soon after the second baby was born. He then examined the pelvic organs and found an old erosion of the cervix and a cystocele that caused the bladder to contain residual urine and some pus. A gynecologic consultant performed the repair necessary to free the pelvic organs of infection. Dermatitis of the hands disappeared permanently, and the positive reaction to patch testing was no longer obtained.

The hands of a retired farmer, 75 years of age, had been inflamed for most of the preceding 50 years. His feet showed no tinea, his tonsils were out, and his prostatic fluid contained no pus. X-rays of the teeth, however, showed numerous root canal fillings and root abscesses. The teeth were extracted, and the hands cleared within two weeks after an initial postoperative flare.

Injections from the Interior Comprising Systemic Disease with Cutaneous Manifestations.—These require discussion when one is considering all possible dermatitides of the hands. Each kind of parasite affords exemplary possibilities of specific etiologic diagnoses: viruses, and recurrent herpes simplex or brachial herpes zoster; rickettsiae, and Rocky Mountain spotted fever; bacteria, and scarlatina, tuberculosis, and syphilis; fungi, and tinea, blastomycosis, or coccidioidomycosis; protozoan infections, and leishmaniasis, and metazoan infections, such as trichiniasis. Successful therapy requires painstaking etiologic diagnosis and then appropriate specific and supportive efforts.

Dermatitis of Unknown Etiology.—This is exemplified by such diseases as the following, which may influence the hands: atopic eczema,[27] lichen chronicus simplex, lupus erythematosus, granuloma annulare, psoriasis, lichen planus, erythema multiforme, scleroderma, and acrosclerosis. In the treatment of these, after one has made the diagnosis, which may require histologic study, empirical therapy offers a good deal.

Pompholyx.—In discussing eruptions of the hands one must include the entity variously designated as pompholyx or dyshidrosis. Much confusion exists concerning the nature of this condition, but its clinical characteristics are fairly typical. The eruption occurs usually on the palms and/or soles and on the sides of the fingers. Initially the process is relatively noninflammatory, consisting of tiny, deep-seated, sago-like vesicles occurring singly or in groups. Later, possibly as the result of secondary infection or irritating medication, the condition may become eczematized and may lose its original character.

Benedek [28] believes that pompholyx is caused by a normally indigenous human micro-organism, Bacillus endoparasiticus, which under ordinary circumstances

26. Sutton and Sutton,[4] pp. 97 and 335.

27. Rowe, A. H.: Atopic Dermatitis of the Hands Due to Food Allergy, Arch. Dermat. & Syph. **54**:683-703 (Dec.) 1946. The author was vastly more enthusiastic about the etiologic significance of food allergy than we are; compare references 12, 14, and 15.

28. Benedek, T.: Pompholyx and Occupational (Contact) Dermatitis, Indust. Med. **16**:334-349 (July) 1947.

causes no clinical manifestations but which, as the result of a disturbance in the immunoallergic balance, can be brought into activity manifested in the form of pompholyx. He believes that contact dermatitis may be such a disturbing factor, and he so explains why proved industrial dermatoses of the hands may continue to manifest activity long after all sources of contact irritants have been eliminated. One of us (R. L. S., Jr.) prefers to think of such cases as being due to secondary parasitism, focal parasitism, nutritional deficiency, medicinal irritation, and psychosomatic influences in various etiologic combinations.

Benedek believes that many cases of prolonged or recurrent pompholyx may be brought under control by a series of intradermal injections of B. endoparasiticus vaccine. His ideas have received little acceptance, but in the absence of any definitely proved cause of this stubborn dermatosis (sweat-gland obstruction being another theory), perhaps final judgment should be deferred. One of us (S. A., Jr.) has been interested in this subject during the past two years and has felt that favorable results have been obtained in some obstinate cases with a course of Benedek's vaccine given at four- or five-day intervals in a continuing dose of 0.1 cc. intradermally over a period of several weeks or months. It is, of course, impossible to state categorically whether the beneficial results observed are due to a specific antigenic effect of the vaccine or to a nonspecific protein effect.

Hyperkeratotic Dermatitis of the Palms.—Mary Smith [29] gave, under the title "Lichen Chronicus Simplex (Neurodermatitis) of the Palms and Soles," an excellent description of what we believe may include an entity constituting a group of cases within the class "dermatitis of the hands of unknown etiology." The condition resembles keratoderma climactericum [13] but does not occur exclusively in women. It comprised perhaps 1% of the cases of dermatitis of the hands observed in the past three years in the practice of one of us (R. L. S., Jr.). All the patients have been adults, the majority of them beyond middle age. Their occupations have been widely assorted, but many of them have been housewives.

The lesions are sharply circumscribed, hyperkeratotic, and nonvesicular. They are homogeneous within their borders and arcuate in outline. They are intensely pruritic and sometimes painfully fissuring. They are generally roughly symmetric in distribution, affecting especially the midpalmar region, and are also occasionally scattered on the volar and lateral aspects of the fingers. Lichen chronicus simplex, indeed, may occur on the hands rarely, but when it does, the dorsum of a hand and some of its fingers, unilaterally, and perhaps the flexure of the wrist, are affected. Lichen chronicus simplex is a deeper disease with greater dermal infiltration, less prone to undergo fissuring and more prone to exhibit excoriation.

In this condition, one observes a brilliant, greenish-white, crisply demarcated fluorescence under illumination with Wood's light. Scrapings and cultures have not yielded positive bacteriologic or mycologic findings, although the lesions of several patients have yielded species of Hormodendrum, the pathogenicity of which is of course questionable. The histologic structure, with parakeratosis and fairly intense, superficially located, leucocytic infiltration of the dermis, resembles somewhat that of psoriasis. Yet psoriatic lesions are not present elsewhere on the bodies of the patients. In the parakeratotic corneum of the tightly adherent and slightly frayed scale, under high magnification, one finds minute, glassy, refractile

29. Smith, M. S.: Lichen Simplex Chronicus (Neurodermatitis) of the Palms and Soles, Brit. J. Dermat. **54**:255-264 (Oct.) 1942.

granules a micron or so in diameter, disposed in rows paralleling the surface, their appearance and arrangement suggesting that they may be fungi. Jeanrette Carter, Ph.D., and one of us (R. L. S., Jr.) have not succeeded in cultivating them, although we tried, among others, one medium containing a considerable amount of macerated human epidermis at pH 7.0. Perhaps they are merely hyaline granules representative of imperfect keratinization. In two patients the total protein of the blood was less than 6.0 gm. per 100 cc.

Smith[29] reported on 25 cases, in many of which she found low blood sugar levels. She offered the hypothesis that the disease may be due to functional attrition of the endocrine glands, especially the adrenals, possibly resulting from chronic emotional strain. Her patients improved with mixed glandular therapy. Some of her patients had also the lesions of lichen chronicus simplex in other locations, such as the commonly affected suboccipital region, a fact which could be merely coincidental. Lichen chronicus simplex was not also present in our cases.

One of us (R. L. S., Jr.) believes these cases exemplify a disease not identical with lichen chronicus simplex or with keratoderma climactericum, of which the original description by Haxthausen,[13] quoted verbatim, evidences clear-cut differences:

> This hyperkeratosis of the palms and soles appears in its earliest stages as discrete, sharply defined lesions of regular form, round or oval in shape, and varying in size from that of a lentil to a pea. These lesions do not project, or only do so to a very slight extent . . . and do not cause itching. The horny layer is often slightly frayed and sometimes crossed by superficial fissures, but in the early stages there are no miliary vesicles or other evidence of eczema formation. When the affection has persisted for some time, it may become complicated with eczema, especially in the palms, and moderate itching may then, in some instances, occur. On eczematization the original sharply defined lesions become less clear in outline and in places confluent, particularly in the middle of the palm, giving rise to irregular-shaped hyperkeratotic patches with miliary vesicles, weeping base, and deep fissures. The skin beyond the part actually affected is in many cases remarkably dry, and not rarely shows a mild diffuse thickening of the horny layer with accentuation of the natural folds. . . . The course . . . is at first entirely symptom-free. . . . It is not until the frequent complication of eczema has arisen that the skin affection causes the patient to seek medical advice. . . . Searching examination of these patients reveals that the skin affection in question arises under certain definite circumstances, and that it is accompanied by distinctive general symptoms. . . . It is possible in most cases to determine, in addition to the cutaneous affection, symptoms which are to be regarded probably as links in the collective clinical picture, such symptoms in particular as *obesity* and arterial hypertension with, less frequently, arthritis of the knee joints. . . . With regard to treatment of the skin affection, this is rather disappointing. . . . The symptom causing the greatest inconvenience, namely, the frequent eczematization occurring particularly upon the palms, can usually be brought fairly readily under control. While it may be necessary in some of the advanced cases to apply cold boiled water compresses for a few days, it is usually possible to start treatment straight away with ointments, of which Vaseline® is the most suitable, or a mixture of Vaseline® and lanolin with the addition of 1 to 10 percent salicylic acid. . . . To obtain a satisfactory result, it is important that the patients entirely avoid washing and contact of any sort with water over a long period. For internal medication we have tried thyreoidin and various ovarian preparations, but the effect of these drugs has not been very convincing. At any rate, we did not succeed by these means in producing a definite cure in any single case—that is to say, a complete disappearance of the keratosis.

In our particular kind of circumscribed, pruritic, hyperkeratotic dermatitis of the palms, one does not observe the sudden flare phenomenon which occurs in

30. Smith, S. W.: Eczema Autolytica, Brit. M. J. **1**:628 (May 5) 1945. Sutton and Sutton,[4] p. 492.

"autolytic eczema" as described by S. W. Smith[30]; the "autosensitization dermatitis" of Templeton, Lunsford, and Allington,[31] or the "autoeczematization" of Cormia and Esplin,[5] the phenomenon characterized by widespread, erythematous, and vesicular rash typically associated with lichen chronicus simplex under the influence of irritation, maceration, or secondary infection. This hyperkeratotic dermatitis remains dry and limited to the palms, fingers, and distal volar skin of the wrist.

Ayres and Anderson[32] described "hyperkeratotic dermatitis" and warned against mistaking it for contact dermatitis.

Some patients have been benefited by the avoidance of contactant irritants (especially the harsh cleansers), the use of bland cool compresses, the restriction of caffeine ingestion, the generous administration of vitamins, moderate doses of x-ray therapy, and ammoniated mercury ointment, U. S. P. The topical application of other antibacterial and antifungus medicines has not seemed beneficial. A few patients appeared to be helped by a vanishing cream incorporating estrogen.

We hesitate to present "circumscribed, pruritic, hyperkeratotic dermatitis" as an entity, feeling that there are not sufficient data on which to base a conclusive proof of its distinction from other diseases. Excerpts from our correspondence during the preparation of this paper may be of interest:

R. L. S., Jr.: I think there is a hyperkeratotic dermatitis of the palms which is not malformation, psoriasis, seborrheic dermatitis, lichen chronicus simplex, keratoderma climactericum, contact dermatitis, or tinea. One can circumscribe its typification by designating what it is not.

S. A., Jr.: I have been encountering such cases over a period of years, but I have never felt that I was dealing with an entity. I am not at all sure that there is a consistent clinical picture. It seems to me that the lesions in my cases have varied from rather sparse, ill-defined lesions on the palms or palmar and lateral surfaces of the fingers to more sharply defined, thicker and more inflammatory lesions with considerable itching and fissuring. In am not certain that I could differentiate between keratoderma climactericum, contact dermatitis due to grasping some object to which a patient was sensitive, a palmar eruption which might be due to a metabolic disturbance, such as vitamin A deficiency or impaired liver function, or even an atypical psoriasis of the palms.

One may safely, however, recognize the existence of a class of dermatoses involving the palms which is characterized by hyperkeratosis, often with itching, fissuring, and in some cases, erythema. Among such cases one sees various grades of these various features, so that it is difficult to decide whether there exists among them a subgroup with a specific clinical picture. One of us (R. L. S., Jr.) leans toward the view that a specific picture may be drawn, delineated by the features of sharp margination; lesions which are oval, homogeneous, and superficial; absence of vesiculation; presence of marked pruritus; unresponsiveness to mere control of

31. Templeton, H. J.; Lunsford, C. J., and Allington, H. V.: Autosensitization Dermatitis: Report of 5 Cases and Protocol of an Experiment, Arch. Dermat. & Syph. **59**:68-77 (Jan.) 1949. Sutton and Sutton,[1] p. 492.

32. Ayres, S., Jr., and Anderson, N. P.: So-Called Fungus Infections of the Hand, California & West. Med. **56**:63-66 (Feb.) 1942. Of these authors' cases of dermatitis of the hands, 88% were not tinea. They discussed a multiplicity of varieties of dermatoses of the hands: dermatophytids, dermatophytosis, yeast infections, dermatitis venenata, bacterial infections, virus infections, scabies, recalcitrant vesiculopustular eruptions, eczema, pompholyx,[4] hyperkeratotic dermatitis,[29] syphilis, and miscellaneous conditions, including psoriasis, lichen planus, erythema multiforme, tuberculosis, and cancer.

contactants; absence of the autoeczematization phenomena which often accompany lichen simplex chronicus and lack of the thickness and the occasional moisture of this condition; distribution of peculiar limits, and manifestation of an interesting fluorescence in Wood's light.

NONINFLAMMATORY DERMATOSES OF THE HANDS.—Not to be construed as, strictly, "dermatitis" are numerous other dermatoses often affecting the hands, such as epidermolysis bullosa, keratosis palmaris hereditaria, keratoses, and carcinomas. Metabolic disorders, such as acanthosis nigricans and xanthoma, seem to belong in this classification rather than with dermatitides due to internal chemical influences.

COMPLEXITIES OF ETIOLOGY

Dermatitis of the hands is not often due entirely to one mechanism.[33] Take for example an inflammation resulting from excessive exposure to sunshine. Redness and vesiculation follow, new epidermis is supplied from beneath, epithelization becomes regular after a period of irregularity manifested by scaling, the dermal reaction is reversible and fades in due time, and the skin again becomes normal. But complications are possible. An unfortunately chosen sunburn remedy might act as a sensitizer. The person would then have his physical injury plus superimposed dermatitis venenata. The lesions easily could become infected with pathogenic micrococci, and he then would have bacterial dermatitis as well. He might, therefore, be given injections of penicillin and break out with dermatitis medicamentosa. If his luck continued bad, his pyorrhea might serve to reinfect his dermatitis more or less continuously. Then he might be given some x-ray therapy, improve for a time, relapse, receive more x-ray therapy repetitiously, and eventually suffer x-ray burns. A conceivable sequence of events in a woman patient might be outlined as constipation, laxative, phenolphthalein eruption, excoriation, sulfonamide salve, sulfonamide sensitization, and sulfonamide-resin nail-lacquer dermatitis enduring unrecognized, with attendant suffering, loss of time, medical expense, and the likelihood of still further complication.

Dermatitis of the hands is seldom a simple thing etiologically, and, in the study of any case, the person as a whole and his environment as a physiochemical and sociobiologic complex may have to be taken into account.

MANAGEMENT OF CHRONIC DERMATITIS OF THE HANDS

When one sees, then, a case of dermatitis of the hands of obscure etiology, in contrast to the cases of easy interpretation and in contrast to cases of some recognizable traditional entity of unknown etiology, such as psoriasis, the procedure that

33. (*a*) Barber, H. W., and Eyre, J. W. H.: Acrodermatitis Continua (Hallopeau) vel Dermatitis Repens (Crocker), Brit. J. Dermat. **39**:485-520 (Dec.) 1927. (*b*) Mitchell, J. H.: Amycotic Dermatoses Simulating Ringworm and Erosio Interdigitalis Blastomycetica, Arch. Dermat. & Syph. **19**:659-670 (April) 1929. (*c*) Ringworm of Hands and Feet: Historical Review, J. A. M. A. **146**:541-546 (June 9) 1951. The author makes clearly the point that coccic infections produce vesicular and pustular disease of the palms and fingers. One must accept as mycotic only those cases in which fungi can be found. (Compare Ayres and Anderson.[32]) (*d*) Sulzberger, M. B., and Baer, R. L.: The 1948 Year Book of Dermatology and Syphilology, Chicago, Year Book Publishers, Inc., 1948, pp. 7-44. (*e*) Carpenter, C. C.: Management of Recurrent Vesiculopustular Eruptions of Hands and Feet, J. M. Soc. New Jersey **42**:262-267 (Aug.) 1945. (*f*) Winston, B. H.: Dermatitis of the Hands, Arch. Dermat. & Syph. **57**:357-367 (March) 1948. (*g*) Samitz, M. H.: Eczematous and Pustular Eruptions of the Hands, ibid. **59**:145-149 (Feb.) 1949. Ayres and Anderson.[32]

we utilize follows upon the attempt to answer the question, "What keeps this patient from getting well?" Is the skin repetitiously injured by chemicals it touches? Are parasites locally reproductive, or are they continually fed into the region from foci of infection, so that the patient's lesions cannot heal? Is the patient's inability to mend due to nutritional or metabolic deficiency? "Lowered resistance"[9] takes on added meaning when it is interpreted in the light of protein nutrition and liver function.

It is the physician's job to create the optimum circumstances which favor healing, and that is all he can do. "Chronic" dermatitis of the hands may be said, arbitrarily, to exist when disease has persisted for two months or more. Cases of such duration are, practically speaking, always due to a complex of etiologic factors. The following efforts, then, are appropriate and broadly inclusive.

1. See to it that no physical agencies or nervous hypermotility and excoriation interfere with healing. Instruct the patient regarding the need for quiet, rest, and relaxation. Help him to allay anxieties and practice amateur psychiatry if indicated. Do not withhold sedation.

Caffeine is a stimulant of the nervous system, and the skin is a peripheral ectodermal organ of sensation capable of being made irritable by the drug, as the central nervous system is. Caffeine interferes with sedation and rest. A given quantity of itching is less tolerable and more annoying when the patient is overstimulated. Caffeine is often used by a hypothyroid patient to mask his symptoms of hypothyroidism. Such persons are well served by the physician's substituting the right dose of thyroid for the wrong dose of caffeine. Balancing the physiologic dose of thyroid is impossible when caffeine is being taken in excess. We deem it advisable for these reasons to restrict severely the ingestion of coffee, tea, and the cola drinks by patients with chronic dermatitis.

2. See to it that no chemical likely to irritate the skin touches the hands. Allow contact only with water, cotton, linen, and carefully selected, rarely irritating medicines, such as aluminum acetate or boric acid, a teaspoonful to the quart of water, for cool compresses, and petrolatum or phenolated zinc paste.

The elimination of contactant irritants can be accomplished by following a technic one of us (R. L. S., Jr.) described,[34] which is based on the fact that, although at first one does not know the cause, one can probably eliminate it by eliminating everything that is likely to be causative. The skin heals of its contactant injury usually within a week or two of inconvenient living in chemical isolation or fails to heal if the elimination is not successful, in which case the eliminative effort must be intensified until exclusion of the unknown cause does succeed, even if this requires hospitalization. Then the chemicals with which the patient desires to come into contact are replaced upon his skin in an orderly fashion, one each day, so that the flare which follows application of the irritant serves to identify it. During the period of isolation, the patient washes only with water and allays itching with cool water, boric acid, or aluminum acetate compresses, along with petrolatum as a lubricant and sedation with barbiturates or chloral. Note the similarity of method

34. (*a*) Sutton, R. L., Jr.: Contact Dermatitis: Simplification of Therapy and of Search for Causes, J. Missouri M. A. **44**:481-484 (July) 1947; (*b*) Contact Dermatitis: Practical Management and Identification of Cause Without Patch Testing, Arch. Dermat. & Syph. **59**:36-44 (Jan.) 1949. Compare Sutton[34a] and Sutton and Sutton,[4] p. 94.

in identifying contactants by single-item addition to that of identifying food allergens by the single-food additive diet.[35] This technic can be used effectively.

Patch testing, properly carried out and properly interpreted, yields valuable information and may speedily supply data which the use test described above would in some circumstances yield only in a relatively cumbersome way. It has been the practice of one of us (S. A., Jr.) to perform patch tests with various medicines and ointment bases which it may be planned to use on the patient in the course of treatment. Pretreatment patch tests with therapeutic agents have been advocated by Goodman and Sulzberger[36] and by Sulzberger and Baer,[37] who assessed this form of testing as "of inestimable value in the management of allergic dermatoses." These patch tests may be done at the time of the patient's first visit. Even such seemingly innocuous substances as petrolatum, hydrous wool fat, Aquaphor (oxycholesterol-petrolatum), and iodochlorhydroxyquin ointment may at times cause trouble, and in some instances in which preliminary patch tests have not been performed, embarrassment has followed. An appreciable number of cases of contact dermatitis occur in which activity of disease is maintained as a result of intolerance to simple ointment bases.

3. Eliminate coccic parasites as nearly as possible with such means as iodochlorhydroxyquin cream, 1:4,000 potassium permanganate, 2% aqueous methylrosaniline chloride, gentle débridement, 2% ammoniated mercury paste, aureomycin or bacitracin ointment, a sulfonamide or oxytetracycline (Terramycin) administered by mouth, or penicillin given by injection. One of us (R. L. S., Jr.) has been using with much satisfaction a mixture of 2% sulfur and 6.7 mg. of chloramphenicol per gram in iodochlorhydroxyquin cream as a topical antiseptic, with a wide range of effectiveness against cutaneous pathogens of several kinds and a low index of sensitization. We have had little success with autogenous vaccines, and staphylococcus toxoid became largely outmoded when the antibiotics and iodochlorhydroxyquin proved so effective.

4. Eliminate all focal infection, with due attention to feet as sources of dermatophytids, teeth and gums, tonsils, prostate, uterine cervix, and bladder. Some consultants who hold a D.D.S. degree do not know oral infection when they stare at it, and some gynecologists fail to cure an erosion of the cervix or to achieve a shipshape cystocele repair. This situation makes it necessary for the dermatologist to choose his consultants rather than to allow the patient freedom of selection in the matter. Abnormal intestinal bacteria, as well as protozoa, have been known to cause eruptions of the hands, and if present they require identification and suitable therapy.

5. Promote optimum capacity to heal in the patient himself by insuring adequate nutrition, with respect to both vitamins and protein. When appropriate, Guy and associates[18] would prescribe a prosthesis to assure adequate mastication, a diet rich in protein, perhaps the administration of protein hydrolysates, correction of

35. Winston, B. H., and Sutton, R. L., Jr.: Urticaria: Detection of Ingested Allergens; The Single Food Additive Diet, Practitioner **160**:347-352 (May) 1948.

36. Goodman, J., and Sulzberger, M. B.: Patch Tests with Therapeutic Agents, Arch. Dermat. & Syph. **35**:944-945 (May) 1937.

37. Sulzberger, M. B., and Baer, R. L.: The 1943 Year Book of Dermatology and Syphilology, Chicago, Year Book Publishers, Inc., 1943, p. 46.

hypochromic or macrocytic anemia, use of dilute hydrochloric acid with meals, and local care in keeping with the status of the inflammatory process. Give due consideration to liver function and to hormonal equilibrium.[19]

6. Consider the advisability of investigating food allergy by single-food additive dieting, but estimate this effort as statistically unlikely to prove fruitful and as partaking of the nature of "grasping at a straw." Skin tests are seldom of value[38] in seeking food allergies, despite their real value in investigative and theoretical medicine. One of us (S. A., Jr.) employs scratch tests in selected cases in which the history and clinical appearance point to the possible diagnosis of atopic dermatitis. Although disappointments are frequent, occasionally valuable clues are turned up.

7. Hold back on x-ray therapy and use it conservatively, by necessity rather than by whim. X-ray therapy is necrobiotic, but it does not kill parasites. It has cumulative effects which can cause serious harm, harm which is especially serious when the hands are damaged, for they contain no skin to waste. Yet x-ray therapy induces resolution of inflammation and so may have great value in palliation. It seems temporarily to achieve nonspecific desensitization of the skin, and it usually allays itching symptomatically, inducing vesiculation to dry up.

When x-ray therapy is applied to a vesicular dermatitis and that dermatitis gets worse promptly, bacterial cultures will probably show that Micrococcus aureus are at work (R. L. S., Jr.), and one may surmise that antibiotics may meet with success. In lichen chronicus simplex one would be hard put to it to bring about a cure without x-ray therapy.

X-ray therapy obviously should be carried out only by one thoroughly qualified in this field; yet radiologists have no business to be in charge of a case of dermatitis, for they simply do not know enough dermatology. Dermatologists, on the other hand, are obliged to know enough radiology to use the tool correctly—as they must likewise be able to use a scalpel correctly—in the therapy of dermatoses. A dermatologist, furthermore, has to know enough about radiology, and possess wisdom enough, to stay out of trouble.

SUMMARY

Inflammatory dermatoses of the hands are etiologically heterogeneous. An etiologic classification is presented in some detail. In some cases the condition is contact dermatitis, in some it is primarily bacterial or fungous in origin, in some it is due to the admixture of contactant and parasitic activity, in some it depends on focal infection, in some it is due to defective nutrition and metabolism, in few indeed it is due to food allergy, and in some it is of unknown cause. Etiologic factors frequently work in combinations.

In difficult and chronic cases of mixed and confusing etiology, medical management requires the effort to unravel the complexities so that they can be defeated in detail. Treatment should be directed at controlling all influences which may be interfering with healing. In a problematic case the dermatosis is likely to respond successfully if the physician achieves at one time (1) elimination of contactants, (2) elimination of parasites, (3) elimination of focal infection, and (4) elimination

38. Lane and associates.[2] Jordan, Dolce, and Osborne.[3]

of defects in nutrition and metabolism with especial reference to vitamins, proteins, liver function, and hormonal balance. Use of the safest medicines one can select for topical application, avoidance of overtreatment, and wisdom in the use of roentgen therapy are advised. Vesiculopustular dermatitis of the hands is seldom fungous infection, but is usually bacterial infection, which is generally made worse fast by fungicidal medication.

Erosion of the cervix uteri is a common, not an unusual, focus of infection pertinent to chronic dermatitis of the hands in women and as such should be looked for in every case.

Overingestion of caffeine has an importantly deleterious effect in promoting irritability of the skin, accumulation of fatigue, and chronicity of dermatitis.

There is a peculiar kind of circumscribed, pruritic, hyperkeratotic dermatitis, here described, which affects the palms and is of as yet undetermined etiology.

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ADDENDUM

If this essay were to be amended to accord with views current in September, 1953, a paragraph would be required for discussion of therapy with cortisone, corticotropin, and hydrocortisone ointment. These drugs have great value in palliation in selected cases, especially those of the "chronic lichenoid type."

ABSTRACT OF DISCUSSION

Dr. Francis W. Lynch, St. Paul: With limited time one cannot thoroughly review a presentation covering so large an area of practical dermatology. Several points, only, can be considered, the first relating to classification. Under the heading "unknown cause" the authors give special consideration to two types: vesicular and psoriasiform. They disagree on dyshidrosis (pompholyx)—as do so many dermatologists—and I shall not comment further on that disorder. More time was given to consideration of sharply marginated hyperkeratotic dermatitis of the palms, more superficial than lichen chronicus simplex and with a greater tendency toward fissuring, resistant to treatment, and resembling keratoderma climactericum but occurring in both sexes. I think we shall all agree as to the existence of such dermatitis in not inconsiderable numbers of cases. With etiologic reference they observed peculiar fluorescence but no significant bacteriologic or mycologic evidence, and the histologic structure only "resembled" that of psoriasis. It is my belief that such cases represent a phase of neurodermatitis (atopic dermatitis) allied to lichen chronicus simplex (but not truely lichenified) and to keratoderma climactericum, which I regard as a variant of neurodermatitis occurring chiefly, but not exclusively, in patients with hypoestrogenic features (Arch. Dermat. & Syph. **48**:270, 1943). Mary Smith similarly grouped such cases with those of lichen chronicus simplex and emphasized the endocrine factors. I question the wisdom of sharply defining the dermatosis in such cases and placing it apart from other dry forms of neurodermatitis (atopic dermatitis).

I thoroughly agree with the authors' statement that chronic dermatitis of the hands is "seldom a simple thing etiologically" and with their attitude in asking in each case, "What keeps this patient from getting well?" I, too, have little faith in so-called allergic study, little hope for results from the usual form of its application, or little charity for some of those who use this approach so freely and extensively (or shall I say expensively for the patient?). With the authors, I agree that three sets of influences frequently delay healing and that in vigorously attacking one of these influences one must not disregard the others. As might be expected, we are in less agreement as to the relative importance of each of these influences and the most satisfactory attack on them.

Sutton has previously discoursed on the importance of chemical contacts and a method of eliminating "all" exposures to such agents temporarily and then observing the results of deliberate exposure to single agents in sequence. For most of my patients this approach seems

impractical. In fact, in the absence of bright redness, swelling, and oozing I make little point of protecting the hands against the ordinary exposures to soap, water, and similar substances commonly regarded as hazards. In practice I believe one can usually recognize those patients whose dermatitis of the hands is primarily or chiefly due to such agents.

With reference to local (topical) infection, I agree as to its frequent incidence and the importance of attacking it vigorously, sometimes repeatedly. On focal infection our views differ. They say their method "makes sense in theory and succeeds in practice" but I regard the experimental evidence as too slight and the results of so-called "elimination" of foci as unpredictable. Yet it will not surprise me if the future proves that a significant association exists between focal infection and many infectious eczematoid processes.

A third set of principal etiologic influences is attacked by attention to the "whole" patient, which Sutton and Ayres would supply by offering adequate nutrition and improving hepatic function. With few exceptions my patients seem adequately nourished, and I find it difficult to measure or evaluate their hepatic dysfunction, but I agree that one should do all one can to improve the general health of the patient. My views are already sufficiently known relative to the importance of psychologic and emotional factors and, in the period of the climacteric, the help to be obtained from estrogenic therapy, not only in treating hyperkeratotic dermatitis but in treating many functional dermatologic disorders of women in the climacteric period.

To summarize briefly, Sutton and Ayres have extensively reviewed a subject of major dermatologic importance, clearly stated their views on the complexity of the etiologic factors, and outlined a therapeutic approach which requires careful and skillful attention to multiple factors. Their paper is a highly significant contribution.

DR. GEORGE C. ANDREWS, New York: The more I see of eruptions on the hands, the less importance I attach to the morphologic appearance. One can get so many misleading impressions from the morphologic characteristics of the hands. The distribution of contact dermatitis is very important—the position of the eruption, or what part of the fingers or hands is involved. There are eruptions of contact dermatitis due to rubber; cement produces eruptions on the soles of the feet which resemble pustular bacterid, pustular psoriasis, or fungous infection. One sees fungous infections on the hands which look exactly like some of the other conditions mentioned; one can see streptococcic acrodermatitis with pustules, bullae, vesicles, and even large bullous eruptions on the palms, which look exactly like acute fungous infection but which yield no fungi and which clear up in two or three days with penicillin injections or use of other antibiotics.

The dermatologist can see all these different things that look alike, and he cannot tell until he studies them and does laboratory work just what they are. One has to make serious studies four or five times to rule out fungous infection. Then one does blood counts and cultures. One makes all kinds of tests for contactants, especially for plastics and rubber cement and various things in shoes, before one can determine the cause. One cannot make a diagnosis by looking at a patient.

In illustration, I had a patient recently who had a subcutaneous noninflammatory cyst on the proximal phalanx of the right index finger. I thought that possibly it was a fibroma, but removal showed that it contained a tremendous quantity of Actinomyces, a most unexpected finding. I think of Dr. Arnold when he said that he was perplexed in the diagnosis of bacterid. One cannot tell what it is by looking at it. I have seen eruptions of the vesicular type on the dorsums of the fingers that looked like contact dermatitis but cleared up after removal of focal infection. One has to study and gradually reach a conclusion as to the diagnosis.

DR. SAMUEL AYRES JR., Los Angeles: We appreciate the discussion that has been given. Dr. Sutton and I have enjoyed collaborating on this paper. I might more properly say I have enjoyed cooperating with Dr. Sutton. The collaboration was a little cumbersome by mail and on one occasion by a rather extended long-distance telephone call, but I think we got together on our ideas, and while the body of the paper may show that there is some difference of opinion here and there, I think we can say that we agree on more things than we disagree on.

In a large proportion of cases, dermatitis of the hands is due to irritation from soap, detergents, and other common household irritants, such as wax, polish, bleach, and solvents, and avoidance of soap and water is one of the first things I would insist upon. Dermatologists sometimes take it for granted that in an acute inflammatory condition the patient should under-

stand such fundamental principles, yet unless explicit instructions are given, one may find out a couple of weeks after an interview that the patient has been scrubbing his hands rather vigorously with soap and water.

Again I should like to emphasize the importance of pretesting any local medication, even an ointment base, that one proposes to use, because sometimes the simplest things may keep the patient's condition active.

Also, regarding Dr. Lynch's discussion on focal infection, we encounter many patients in whom we feel that a focus of infection may be important, but it is not always easy to find the focus. The focus of infection is not necessarily in the teeth or in the tonsils. It may be in the urinary or gastrointestinal tract and may require considerable effort to determine that fact.

One of my physician patients came to me over a period of months with an itching dermatitis of his hands which we felt was probably a contact dermatitis. He was a surgeon, and we tested everything which he was aware of handling, without results. I met him a few months later at lunch, and he showed me his hands, which were well. He stated that an internist had suggested that there might be a focus of infection in the intestinal tract, and though investigations did not reveal any abnormality, treatment with chlortetracycline (aureomycin) and succinylsulfathiazole (Sulfasuxidine) for severeal weeks was followed by complete clearing of his eruption, which has not recurred in over a year. This fact would suggest that a focus of infection in the intestinal tract had something to do with the hand eruption.

I agree with Dr. Lynch in regard to the value of the sex hormones in some cases of hyperkeratotic eruptions, particularly in older persons of both sexes. I agree with Dr. Andrews with reference to the variability of the clinical appearances of hand eruptions from various causes, and I am not quite so certain as Dr. Sutton is of establishing hyperkeratotic eruptions as a definite entity. I would rather speak of hyperkeratotic dermatitis of the hands, including in parentheses the etiology if discovered.

I think the situation is much like that described by Drs. Randall, Kierland, and Montgomery in the Archives of Dermatolgy and Syphilology (Pigmented Purpuric Eruptions, **64**:177-191 [Aug.] 1951), in which purpuric dermatitis of the legs is often presented under a variety of diagnoses. Dr. Randall and associates felt that these diagnoses often represented variable manifestations of the same process, and I would thoroughly agree with that hypothesis.

Trichophyton purpureum infections are always to be considered and ruled out in any case of scaling or hyperkeratotic eruption of the hands.

I should like to emphasize the importance of considering impaired liver function. Sometimes fairly extensive impairment of liver function may be revealed by a sulfobromophthalein (Bromsulphalein) liver-function test, even in the case of comparatively mild eruptions, and results from treatment of the dysfunction are often gratifying.

CARCINOMA OF LIMBUS

Report of 19 Cases Treated with Radium and Effect of Gamma Radiation upon Eye

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THERE has been considerable recent interest on the part of dermatologists as to the long-term effects of x-ray and radium therapy used under varying conditions. The absence of undesirable sequelae from x-ray therapy as employed in the treatment of acne vulgaris has been reported by both Crawford [1] and Sulzberger [2] and their respective associates. Callaway [3] and his co-workers investigated the tolerance of the gonads to x-rays. Lehmann and Pipkin [4] have summarized their results with interstitial radium therapy, and Alden, Jones, and Rankin [5] have recorded 15 years' experience in treating inflammatory diseases of the eye with moderate doses of x-rays.

This report deals with carcinoma of the limbus treated with cancerocidal doses of radium. During the past 20 years, 19 patients with such cancers have been treated. This experience has given us the opportunity of studying the effect of gamma radiation upon the eye. The majority of these patients have been followed for at least four years after treatment, and repeated ophthalmologic examinations have been performed.

Before discussing technique and results of treatment and the effects of x-rays and radium rays on the eye, the lesion will be described and the accepted methods of treatment briefly reviewed.

DESCRIPTION OF THE LESION

The term limbus is defined as "a hem or border" [6] and when used in reference to the eye is called the limbus corneae, the limbus conjunctivae, or, more commonly,

Read at the Seventy-second Annual Meeting of the American Dermatological Association, Colorado Springs, Colo., April 26, 1952.

1. Crawford, G. M.; Luikart, R. H., and Tilley, R. F.: Roentgen Therapy in Acne, New England J. Med. **245**:726-728 (Nov. 8) 1951.

2. Sulzberger, M. B.; Baer, R. L., and Borota, A.: Do Roentgen-Ray Treatments as Given by Skin Specialists Produce Cancers or Other Sequelae? A Follow-Up Study of Dermatologic Patients Treated with Low-Voltage Roentgen Rays, A. M. A. Arch. Dermat. & Syph. **65**:639-655 (June) 1952.

3. Callaway, J. L.; Moseley, V., and Barefoot, S. W.: Effects of Roentgen Ray Irradiation on Testes of Rabbits: Possible Harmful Effects on Human Testes from Low Voltage Roentgen Ray Therapy, Arch. Dermat. & Syph. **56**:471-479 (Oct.) 1947.

4. Lehmann, C. F., and Pipkin, J. L.: Interstitial Radium Therapy: Description of a Short Technique, A. M. A. Arch. Dermat. & Syph. **63**:312-322 (March) 1951.

5. Alden, H. S.; Jones, J. W., and Rankin, J.: Roentgen Ray Treatment of the Eye: Further Experiences, Arch. Dermat. & Syph. **59**:430-434 (April) 1949.

6. Dorland, W. A. N.: The American Illustrated Medical Dictionary, Ed. 12, Philadelphia, and London, W. B. Saunders Company, 1924, p. 612.

simply the limbus. It is an "area 1 mm. wide which marks the transition between the cornea on one hand and the conjunctiva, the episclera tissue, and the sclera on the other." [7] The epithelium is thicker and more irregularly arranged than that of the adjacent cornea. New growths occurring at the limbus are more frequent in the portion exposed by the palpebral aperture. Ash,[8] in a review of 1,120 cases of epibulbar tumors in the files of the Armed Forces Institute of Pathology, found

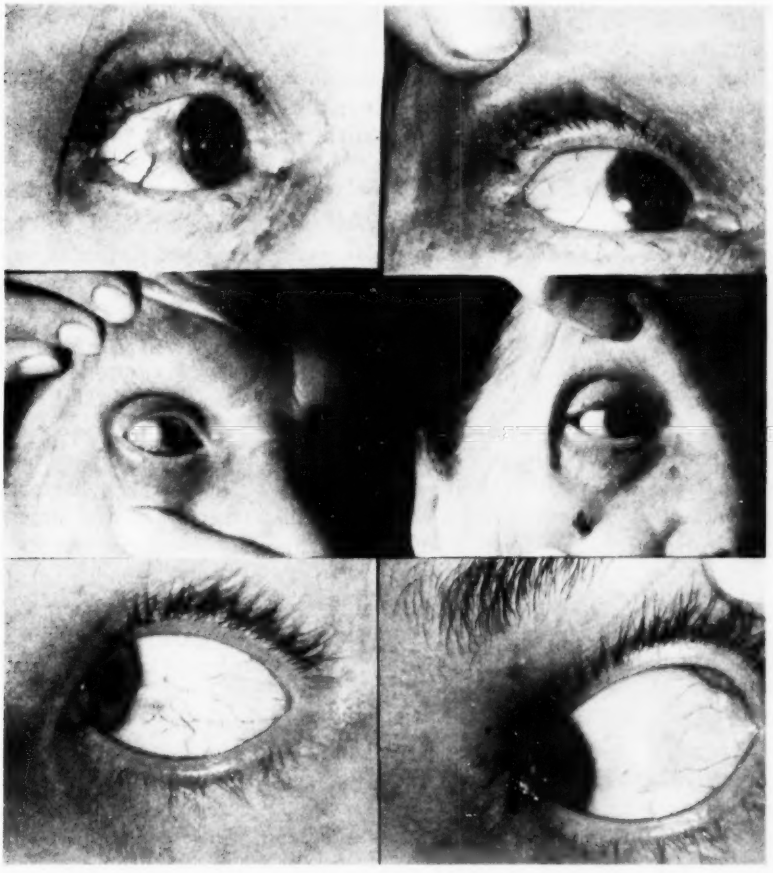

Fig. 1.—Carcinoma of the limbus before and after treatment. Top row, Case 19; Center row, Case 17; Bottom row, Case 18.

282 lesions occurring at the limbus, 68 of which were diagnosed as squamous-cell carcinoma and 3 as basal-cell carcinoma. Other lesions found at the same site were papillomas, epidermidalization with and without dyskeratoses, nevi, malignant melanomas, dermoids, dermoid cysts, teratomas, pterygia, and pingueculae. Carcinoma

7. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. 1, St. Louis, C. V. Mosby Company, 1932, p. 45.

8. Ash, J. E.: Epibulbar Tumors, Am. J. Ophth. **33**:1203-1219 (Aug.) 1950.

occurs more frequently in elderly men at the temporal portion of the limbus (Fig. 1). It first appears as a whitish or grayish slightly elevated patch and must be differentiated from leucoplakia. Slowly the growth increases in size and becomes sessile or warty in appearance and is firmly fixed to the underlying tissue. Along with this growth there is a marked increase in the vascularity of the lesion.[9] Prominent conjunctival vessels course toward the tumor. The growth tends to be proliferative rather than invasive, and as it increases in size the tumor spreads over the cornea and sclera and finally protrudes as a fungating mass between the lids. Extension to the underlying structures is slow because of the density of the cornea and sclera and the paucity of lymphatics.[10] Metastasis is rare, although recurrence after surgical removal is not unusual. Upon microscopic examination the majority of the growths are found to be squamous-cell carcinomas.[10]

METHODS OF TREATMENT

Surgical removal, irradiation, or a combination of the two procedures all have their advocates. Duke-Elder[10] recommends excision followed by exposure to radium or x-rays except in the case of small lesions which may be widely excised. Reese[11] advises simple excision of the lesion, although he considers postoperative beta radiation or contact x-ray therapy justified if the underlying sclera is found to be involved at the time of the operation. Swan, Emmens, and Christensen[9] have observed a relatively high incidence of recurrence after excision when the conjunctival and corneal stroma were involved. In such cases, they advocate postoperative contact x-ray therapy. Ash and Wilder[12] advise against irradiation, recommending local excision and enucleation only if recurrences persist. In 23 of their 48 reported cases enucleation was performed. Numerous other observers[13] have reported successful treatment of carcinoma of the limbus with x-ray or radium therapy.

TECHNIQUE OF TREATMENT

The method of treatment employed in these cases was first observed in the office of Dr. C. M. Griswold, of Houston, Texas. The patient lies on a treatment table, and the eye is anesthetized. After anesthesia is complete, an eye speculum is placed under the lids, and the patient is directed to focus on a spot on the opposite wall. The radium is placed on gum rubber, which, in turn, is applied directly to the lesions (Fig. 2). A nurse sits by the patient and keeps the cornea moist with boric

9. Swan, K. C.; Emmens, T. H., and Christensen, L.: Experiences with Tumors of the Limbus, Tr. Am. Acad. Ophth. p. 458-469, May-June, 1948.

10. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. 2, St. Louis, C. V. Mosby Company, 1938, pp. 1783-1786.

11. Reese, A. B.: Tumors of the Eye, New York, Paul B. Hoeber, Inc., 1951, p. 26.

12. Ash, J. E., and Wilder, H. C.: Epithelial Tumors of the Limbus, Am. J. Ophth. **25**:926-932 (Aug.) 1942.

13. (*a*) Johnson, F. M.: Treatment of Carcinoma of the Conjunctiva with Radium, Am. J. Ophth. **7**:589-595 (Aug.) 1924. (*b*) Evans, S. D.: Carcinoma of the Limbus, Arch. Ophth. **27**:1132-1134 (June) 1942. (*c*) Grenier, E. D.: Epithelioma of the Limbus, Canad. M. A. J. **42**:428-430 (May) 1940. (*d*) Lamb, J., in discussion on Alden, Jones, and Rankin, J.[5] (*e*) Sykes, E. M.: Interstitial Irradiation Therapy in Carcinoma Originating at the Limbus, Texas J. Med. **42**:376-380 (Oct.) 1946. (*f*) Griswold, C. M., in discussion on Sykes.[13e]

acid solution. Ten to 14 days after treatment a moderate amount of conjunctivitis develops, but, in this series of cases, this complication has not been particularly incapacitating. The growth disappears very rapidly, and the reaction subsides about six weeks after treatment.

In three cases of this group there was treatment with beta radiation using a radium plaque made up of five Monel metal needles, each containing 5 mg. of radium and having a wall thickness of 0.25 mm. They were placed side by side on 1 mm. of rubber and applied to the lesion for 20 or 30 minutes (depending on the thickness of the lesion) on three occasions at three-day intervals. For the rest, or 16 cases, there was treatment with gamma rays. Two 25 mg. tubes with an external diameter of 2.5 mm., 9 mm. active length, and a wall thickness of 0.5 mm. of platinum were used. These were placed parallel to each other on a sufficient thickness of gum

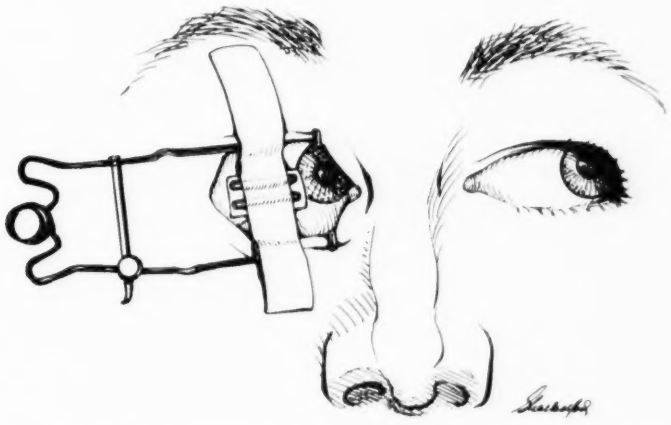

Fig. 2.—Method of application of two 25 mg. radium tubes to the lesion.

rubber to give the desired dose to the base of the tumor. This required two to four treatments of approximately one hour each at three-day intervals. Since these lesions have proved to be radiosensitive, a minimal cancerocidal dose was employed. If the tumor was fungating, it was found advisable for an ophthalmologist to remove the proliferative mass before treatment. This procedure prevented the lens from receiving an unnecessary amount of irradiation.

REPORT OF CASES

This series of patients includes 7 women and 12 men with an age range of from 30 to 82 years. The majority of these patients had led outdoor lives and had had more than average exposure to sun and wind. In all the cases the diagnosis of carcinoma of the limbus was made by an ophthalmologist and radium therapy advised.

The results are summarized in Tables 1 and 2. It will be noted that all the patients were cured, although the classic five-year follow-up period was possible in only 11 cases.

TABLE 1.—*Interval from Date of Treatment to Most Recent Ophthalmologic Examination*

Patients, Total No.	Patients Cured, No.	Follow-Up Period, Yr. More than 10	More than 4	More than 1	Less than 1	Possible Radiation Sequelae* Minor	Major
19	19	6	11	15	3	2†	4‡

* Small nonprogressive anterior capsular opacities under treated site that do not interfere with vision.
† Cataracts. In three elderly patients incipient cataracts were present at time of treatment and progressed to maturity. In one patient excessive amount of irradiation necessary for cure resulted in typical irradiation cataract.

TABLE 2.—*Report of Cases*

Case	Sex	Age	Treatment, Date	Most Recent Examination	Gamma* Roentgens to Tumor Base	Gamma† Roentgens to Lens	Comment
1	M	42	2/15/32	5/15/49	Beta radiation used	.....	Cured; no change in vision or evidence of irradiation damage; lost other eye prior to treatment of corneal ulcer and had had several corneal ulcers of treated eye
2	F	50	3/18/32	9/15/32	Beta radiation used	.....	Cured; examination 6 mo. after treatment, vision 20/20; no change from irradiation; died, 1942, of heart disease; no apparent change of vision
3	M	45	9/12/35	11/24/51	3,000	1,100	Cured; correctible vision 20/30; no change from irradiation
4	M	45	10/28/35	9/ 7/51	10/28/35 2,500 1/11/36 2,500	1,100 1,100	Cured; lesion had twice recurred after surgical removal; retreatment necessary owing to inadequate initial treatment; irradiation cataract present when examined 16 yr. after treatment; vision limited to hand motion
5	F	76	4/ 6/38	7/ 7/42	3,300	1,380	Cured; died 6 yr. after treatment from heart disease; although no post-treatment ophthalmologic examination, no change in vision apparent to patient or family
6	F	43	2/15/37	5/21/51	3,300	1,380	Cured; correctible vision 20/20; small anterior capsular opacity under treated area; no change in opacity since 1941
7	F	45	5/ 2/38	8/28/51	Beta radiation used	.....	Cured; correctible vision 20/20; small anterior capsular opacity under treated area which has been stationary for several years
8	F	61	9/21/39	9/17/51	3,000	1,320	Cured; at time of treatment incipient cataract present and corrected vision 20/50; 1 yr. later no change in vision; 4 yr later progression of cataract; vision 20/200; 7 yr. after treatment mature nuclear cataract
9	M	64	7/18/40	9/25/51	3,000	1,320	Cured; corrected vision treated eye 20/40, untreated eye 20/100; no change from irradiation
10	M	54	6/21/42	11/ 1/45	2,937	875	Cured; correctible vision 20/20; no change from irradiation
11	M	70	7/ 8/42	6/12/47	3,375	968	Cured; bilateral incipient cataracts present at time of treatment; bilateral cataracts removed 1947; ophthalmologist did not consider irradiation cause of cataracts
12	F	32	9/20/43	8/22/51	3,060	800	Cured; vision 20/20; no change from irradiation
13	M	35	11/30/46	11/19/51	3,375	968	Cured; vision uncorrected 20/20; no change from irradiation
14	M	34	8/27/47	3/12/51	8/27/47 2,340 11/15/47 2,775	1,140 697	Cured; vision uncorrected 20/20; no change from irradiation; initial treatment inadequate and retreatment necessary
15	M	54	1/ 3/49	9/ 5/51	3,525	1,050	Cured; vision 20/20; no change from irradiation
16	M	79	6/16/49	8/14/49	3,375	968	Cured; no apparent change in vision; died of heart disease, 1950
17	F	82	11/14/49	8/28/51	3,460	1,260	Cured; bilateral incipient cataracts in both eyes before treatment; cataract in treated eye has progressed to maturity; vision now limited to hand motion; irradiation possibly hastened maturity of incipient cataract; no change in cataract of untreated eye
18	M	30	9/29/50	9/31/51	3,375	968	Cured; vision 20/20; no change from irradiation
19	M	72	7/19/51	1/ 8/52	3,375	968	Cured; no change in vision; no change from irradiation

* The distance from the radium source to the base of the tumor and to the center of the lens varied with the interposed thickness of the lesion, and the gamma roentgen dose to each site was calculated on this basis. The gamma dose rate curve on which these calculations were based was found in accord when compared with the results obtained by R. Sievert's method (*Acta radiol.* **11**: 249-267 [Aug.] 1930, and *Acta radiol.* Supp. 14, 1932). This confirmatory work was done by Peter Wootton, B. Sc., American Institute of Physics, Clinical Physicist to the University of Texas M. D. Anderson Hospital for Cancer Research.
† The estimated distance from the limbus to the center of the lens is 5 mm.

As previously stated, three patients were treated with beta radiation and 16 with gamma radiation. The results obtained from the use of beta rays were satisfactory, but owing to the rather intense post-treatment reaction from these rays, gamma radiation was substituted and employed in the other 16 cases of this series. As noted in Table 1, 6 of these 19 patients had changes in the lens or its capsule which appeared at varying intervals after completion of treatment. In two of the six patients small anterior capsular opacities which are stationary and do not interfere with vision developed. One of these two patients was treated with gamma radiation and the other with beta radiation. In the other four patients, all of whom had been treated with gamma radiation, cataracts developed. It is significant that three of these patients had incipient cataracts before treatment; all these patients were elderly. The fourth patient, a 45-year-old man (Case 4) in whom a cataract developed, had no signs of lens change before treatment. He was treated for an extensive lesion of the left lateral limbus which had recurred twice after surgical excision. After removal of the proliferative mass by his ophthalmologist, the area was treated with gamma rays, receiving 2,500 γr. It regressed satisfactorily, but two months later there was a recurrence and additional treatment was given in the amount of 2,500 γr, making a total of 5,000 γr to the base of the tumor and 2,200 γr to the lens. He disappeared from observation, and when he was reexamined 16 years later an irradiation cataract was present, and vision was limited to hand motion.

Effective Dose.—An initial dose of 2,937 and 3,525 γr delivered to the base of the tumor in 3 to 10 days has proved to be curative. For two patients, whose lesions received 2,500 and 2,340 γr respectively, retreatment was required.

COMMENT

The effect of x-rays and radium rays upon the structures of the eye has provoked much discussion in the medical literature without complete uniformity of opinion; however, there is general agreement that any part of the eye can be damaged by these rays in sufficient dose and that the young, immature eye is particularly sensitive. The vast majority of reports concern injury to the lens, and since this is the only part of the eye which has suffered damage following radium therapy in this series of cases this discussion will be confined to the effect of radium and x-rays upon that section of the eye.

A review of the existing dermatologic literature indicates that it is the consensus of opinion that the adult eye is relatively insensitive to x-ray and radium radiation in moderate dose. Lenticular damage was not observed by Lehmann[14] in his 113 cases of carcinoma of the eyelid in which there was treatment with beta radiation. Hailey[15] also reported his experience in treating carcinoma of the eyelid with radium and stated that he felt that the fear of damage to the eye from such treatment was unwarranted, although Ketron[16] and Van Studdiford,[17] in discussing this paper, called attention to the possibility of injury, and Van Studdiford remarked that he had seen patients with injury to the lens capsule from radium. Cole and

14. Lehmann, C. F.: Epithelioma of the Eyelid, Texas J. Med. **27**:422-426 (Oct.) 1931.

15. Hailey, H.: Radium Treatment of Epithelioma of the Eyelid, South. M. J. **27**:681-683 (Aug.) 1934.

16. Ketron, L. W., in discussion on Hailey.[15]

17. Van Studdiford, M. T., in discussion on Hailey.[15]

Driver [18] had no demonstrable complications when interstitial radium needles were used about the eyeball. MacKee and Cipollaro [19] considered the mature eye of adults much less sensitive to x-rays than the eyelids. The only complication noticed by Griswold [13f] in his cases of carcinoma of the limbus in which there was treatment with radium was a temporary flare of a preexisting glaucoma in one case.

Three hundred patients with inflammatory conditions of the eye were treated with x-rays by Alden, Jones, and Rankin,[5] with 120 kvp (half-value layer not stated) being used. The average total dose in their series of cases was 252 r administered in fractional doses of 70 to 120 r at weekly intervals. Three of their patients received 960 r; lenticular damage was observed in only one patient, and this patient had had additional irradiation elsewhere. The discussers of this paper agreed with me in their conclusion that the adult lens seemed to be relatively resistant to irradiation; however, Belisario,[20] who was one of the discussers, warned against the use of hyperintensive doses of gamma rays in the vicinity of the eye.

Desjardins,[21] in reviewing the ophthalmologic and radiologic literature from 1897 to 1931, which was primarily concerned with animal experimentation, concluded that the sensitiveness of the eye to irradiation depended upon the age of the animal. He considered irradiation productive of cataract in the young, immature eye but stated that lenticular degeneration in the mature eye could be produced only by a dose several times that of the erythema dose of the skin. Clapp,[22] Leinfelder and Kerr,[23] Milner,[24] and Poppe [25] are among those who have reported lenticular damage from the use of x-rays and radium. H. E. Martin [26] states that the use of gamma rays about the eye will produce a high incidence of postirradiation cataracts. There are other radium therapists, such as Sharp [27] and Skinner,[28] with wide clinical experience, who consider lens injury quite rare. One cause of this wide divergence of opinion is explained by Reese,[29] who states that irradiation cataract which starts as an opacity at the posterior pole of the lens is more likely to remain stationary than to progress. He stated that, under these circumstances, there is only slight impairment of vision, because patients with a dense opacity at the

18. Cole, H. M., and Driver, J. R.: Radium Dosage and Technique in Carcinoma of the Skin, Am. J. Roentgenol. **33**:682-689 (May) 1935.

19. MacKee, G. M., and Cipollaro, A. C.: X-Rays and Radium in the Treatment of Diseases of the Skin, Ed. 4, Philadelphia, Lea & Febiger, 1946, p. 208.

20. Belisario, J., in discussion on Alden, Jones, and Rankin.[5]

21. Desjardins, A. U.: The Action of Roentgen Rays and Radium upon the Eye and Ear, Am. J. Roentgenol. **26**:643-679 (Oct.); 789-819 (Nov.) 1931.

22. Clapp, C. A.: The Effect of X-Ray and Radium Radiations upon the Crystalline Lens, Am. J. Ophth. **15**:1039-1044 (Nov.) 1932.

23. Leinfelder, P. J., and Kerr, H. D.: Roentgen Ray Cataract, Am. J. Ophth. **19**:739-756 (Sept.) 1936.

24. Milner, J. G.: Irradiation Cataract, Brit. J. Ophth. **18**:497-511 (Sept.) 1934.

25. Poppe, E.: Skin Carcinomata and Their Treatment, Acta dermat.-venereol. **24**:393-416 (Nov.) 1943.

26. Martin, H. E.: Cancer of the Eyelids, Arch. Ophth. **22**:1-20 (July) 1939.

27. Sharp, G. S.: Treatment of Cancer of the Eyelid, J. A. M. A. **111**:1617-1622 (Oct. 29) 1938.

28. Skinner, E. H., in discussion on Hunt, H. B.: Cancer of the Eyelid Treated with Radiation, with Consideration of Irradiation Cataract, Am. J. Roentgenol. **57**:160-180 (Feb.) 1947.

29. Reese, A. B.: Tumors of the Eye, New York, Paul B. Hoeber, Inc., 1951, p. 121, and 122.

posterior pole may have vision as good as 20/30. In two of my cases, Cases 6 and 7, nonprogressive opacities occurred, but have not interfered with vision. Another confusing factor in the evaluation of the effect of irradiation upon the eye is the latent period which ranges from 9½ months to 12 years and averages 2 years.[24] If one accepts this long latent period and the fact that there can be damage to the lens or its capsule without noticeable impairment of vision, it is readily understood that lenticular damage can be ruled out only by complete ophthalmologic examination after an adequate time interval following therapy.

Milner [24] suggests that the lens of one person may be more radiosensitive than that of another. The findings of Cogan and associates [30] tend to confirm this idea. Two and one-half years after the atomic-bomb explosions at Hiroshima and Nagasaki, they examined 231 survivors who were within 1 km. of the hypocenter of the explosions and found only 5 persons with cataracts.

Another point of interest is that lenses suffering from incipient cataracts are apparently more susceptible to injury from irradiation than the normal lens. This has been the observation of others [31] as well as myself.

TABLE 3.—*Effect of Gamma Radiation upon Normal Lenses; Ophthalmologic Examination Six Months to 16 Years with Median of 5 Years After Treatment*

Patients, Total No.	Gamma Roentgens			
	800-1,320	1,837	1,380	2,200
11	8 Cases No damage	1 Case No damage	1 Case Small anterior capsular non-progressive asymptomatic opacity	1 Case Irradiation cataract

The threshold dose productive of irradiation cataract does not seem to be definitely established. Lenticular opacities in the rabbit eye occurred five to seven months after 500 to 600 filtered roentgens energized by 150 to 200 kv. had been received.[32] Poppe,[32c] employing 175 kv. and a half-value layer of 1.18 mm. Cu, observed that the lens epithelium of rabbits regained its normal appearance after receiving 250 to 500 r. Doses over 500 r produced permanent damage but total cataract did not occur after as much as 1,500 r. In Hunt's [31a] series of 100 cases of cancer of the eyelid in which there was treatment with x-ray or radium therapy, opacities of the lens occurred in 5 patients six months to eight years afterward. In one of his patients, to whom a total dose of 775 tissue roentgens (130 kv. and 1 mm. Al filter) had been administered, a beginning cataract developed five years after therapy. In three of his patients treated with radium the lens received 2,400, 1,500, and 1,350 γr and lens changes appeared in six months, eight years, and five years.

30. Cogan, D. G.; Martin, S. F., and Kimura, S. J.: Atom Bomb Cataracts, Science **110**: 654-655 (Dec. 16) 1949.

31. (*a*) Hunt, H. B.: Cancer of the Eyelid Treated with Radiation, with Consideration of Irradiation Cataract, Am. J. Roentgenol. **57**:160-180 (Feb.) 1947. (*b*) Cutler, M.; Jaffe, H. L., and Grossman, A.: Irradiation of the Eye and Protective Devices, Am. J. Ophth. **21**:747-754 (July) 1938.

32. (*a*) Leinfelder and Kerr[23] (*b*) Peter, L.: Studein zur experimentellen Röntgen- und Radiumkatarakt, Arch. Ophth. **125**:428-462, 1930. (*c*) Poppe, E.: Experimental Investigations of the Effects of Roentgen Rays on the Eye, Oslo, Jacob Dybwad, 1942, pp. 65-67.

respectively. No change in vision was reported by patients whose lenses received less than 1,000 γr. Cogan [33] also considered the threshold dose of gamma rays to be about 1,000 γr.

Eleven of my patients with normal lenses at the time of treatment with gamma radiation have been examined ophthalmologically 6 months to 16 years, with a median of 5 years, after treatment (Table 3). In one of these patients, whose lens received 2,200 γr, a cataract developed, and in another of these patients, whose lens received 1,380 γr, a small anterior capsular opacity developed that has not interfered with vision and has remained stationary for 10 years. The lenses of the other nine patients are still clear. They all received 800 to 1,320 γr with one exception; this patient's lens received 1,837 γr over four years ago.

SUMMARY

Nineteen cases of carcinoma of the limbus successfully treated with radium are reported.

The lesion is described and the technique and results of treatment are recorded.

The effect of x-ray and radium upon the eye has been discussed.

Some degree of post-treatment lens damage was noted in 6 of the 19 patients treated. In two patients asymptomatic and stationary opacities developed and in four patients cataracts developed.

In three of the four patients in whom mature cataracts developed incipient cataracts were present at the time of treatment, and all three of these patients were elderly.

In our series of patients a dose of 800 to 1,320 γr did not damage the normal adult lens.

ABSTRACT OF DISCUSSION

DR. C. F. LEHMANN, San Antonio, Texas: My only experience in treating cancer of the limbus is limited to one case. This was a 43-year-old man whose small cancer (about 3 mm. in diameter) was treated with beta radiation by the insertion of needles under the growth at a distance of about 5 mm. from the lens. The eye is still in good condition, showing a small area of telangiectasia with no lens changes 14 years after treatment.

Since my experience is limited, my discussion will be only on the merits of this paper.

Over a period of many years there has developed a popular fear of applying any form of radiation about the eyes. This misconception is perfectly natural, because irradiation in sufficient amount can damage the lens. When one studies the effects, one must consider doses and techniques. Jones, Alden, and Rankin recently have shown that there is no damage to the eye from small doses of x-ray as applied to inflammatory conditions.

There is an incongruity in most reports dealing with highly intensive irradition to the eye because of the lack of correlated estimations of the exact doses that the lens receives. When one uses huge doses of homogeneous radiation (either x-rays or radium), lens changes are expected.

This report of Dr. Seale includes an estimate of the dose that the lens receives, and his studies give us the latitude of dose between the threshold tolerance dose and the cancer lethal dose estimated in gamma roentgens. He estimates that the threshold dose to the normal adult lens is 1,320 γr. A study of his Tables indicates that there is a latitude between this threshold and a cancer lethal dose in which the incidence of lens damage is low. The lowest limbus dose given was 2,937 γr which delivered to the lens 875 γr with no damage after three years in a 54-year-old man; the highest limbus dose was 5,000 γr, which delivered to the lens 2,200 γr and produced a cataract in a 45-year-old man upon examination 16 years later.

33. Cogan, D. G.: Lesions of the Eye from Radiant Energy, J. A. M. A. **142**:145-151 (Jan. 21) 1950.

I have studied the Tables and can find no consistent equation between dose, age of the patient, and the latent period. For instance, in Case 8, the patient, aged 64, received 3,000 γr to the cancer (1,320 γr to the lens) and had a progression of an incipient cataract seven years after treatment, and in Case 9 the patient, aged 64, had no cataract after having received the same dose 11 years previously. It must be noted, however, that the incipient cataracts occurred in elderly persons, and, further, that in Case 14 the patient, aged 34, received 5,115 γr to the limbus (1,837 γr to the lens), and no cataract has developed after four years.

In applying radium in these cases, the essayist had used a technique that is as selective as is possible by direct application of the radium. This reduces the depth (or distance) dose percentage from the point source of irradiation, and, therefore, reduces as much as possible the dose received by the lens.

To explain the converse of this particular factor in radiation therapy—increasing the distance from radiation to the tumor allows a homogeneous radiation through more tissue in a wider area, so that if the source of radiation were further from the tumor the dose to the lens would more nearly approach that given to the limbus.

In summary, this is an excellent addition to our knowledge about effects of irradiation on the eye, and it includes an appraisal of the effective cancer dose, the threshold tolerance dose to the lens, the latent period for development of lens changes, and the age group, and describes an effective method of saving eyes from cancer of the limbus.

DR. EVERETT R. SEALE: Thank you, Dr. Lehmann. The tolerance of the lens to gamma radiation has been of particular interest to me in using radium in the treatment of cancers of the inner canthus, the lower eyelid, and other areas adjacent to the eye. By using isodose tables it is easy to estimate the amount of radiation the lens will receive. If this amount is to be less than 1,300 γr, it is my opinion that radium can be used with safety. However, if the lens is to receive more than 1,300 γr, in my opinion, x-rays should then be used, since a lead eye shield of 1 mm. thickness will filter out 99% of unfiltered x-rays energized by a 100 kv. machine. On the other hand, if radium is used, a lead eye shield of 2 mm. thickness will filter out less than 20% of the gamma rays.

Another point I wish to stress, which has been brought out in the body of the paper, is the importance of pretreatment eye examinations before irradiation is used about the eye. Otherwise, asymptomatic incipient cataracts which are present at the time of treatment and which progress to maturity are quite likely to be classified as irradiation cataracts.

TOPICAL USE OF POLYMYXIN-BACITRACIN OINTMENT IN DERMATOLOGY

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POLYMYXIN B, which is produced by Bacillus polymyxa (Bacillus aerosporus Greer), is a stable polypeptide with marked bactericidal action against many Gram-negative bacilli and especially against Pseudomonas aeruginosa. Variants of polymyxin were announced independently by three groups of investigators: Ainsworth, Brown, and Brownlee;[1] Benedict and Langlykke,[2] and Stansly, Shepherd, and White.[3] These variants, designated A, B, C, D, and E, have similar antibacterial spectra but differ in their amino-acid components and toxicity.

The alteration of the bacterial flora by the widespread use of antimicrobial agents has increased the incidence of Proteus, Pseudomonas aeruginosa (Bacillus pyocyaneus), and Candida albicans as secondary invaders, owing to the elimination of sensitive bacteria and multiplication of these resistant species. This observation is true for the skin as well as for other locations. Owing to the high bactericidal activity of polymyxin B against Gram-negative organisms, conjunctivitis, granulating wounds, and burns infected with Pseudomonas have been successfully treated with this antibiotic in solution, in a cream, and in a petrolatum base.[4]

Since polymyxin B is bactericidal for most Gram-negative bacteria and possibly some fungi,[5] its combination with bacitracin,[6] an antibiotic which is active against Gram-positive organisms, in an ointment base makes available a broad-spectrum bactericidal preparation for topical application.

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1. Ainsworth, G. C.; Brown, A. M., and Brownlee, G.: "Aerosporin," an Antibiotic Produced by Bacillus Aerosporus Greer, Nature, London **160**:263 (Aug. 23) 1947.

2. Benedict, R. G., and Langlykke, A. F.: Antibiotic Activity of Bacillus Polymyxa, J. Bact. **54**:24-25 (July) 1947.

3. Stansly, P. G.; Shepherd, R. G., and White, H. J.: Polymyxin: A New Chemotherapeutic Agent, Bull. Johns Hopkins Hosp. **81**:43-54 (July) 1947.

4. Jackson, D. M.; Lowbury, E. J. L., and Topley, E.: Pseudomonas Pyocyanea in Burns: Its Role as a Pathogen and the Value of Local Polymyxin Therapy, Lancet **2**:137-147 (July 28) 1951. Jawetz, E.: Infections with Pseudomonas Aeruginosa Treated with Polymyxin B, A. M. A. Arch. Int. Med. **89**:90-98 (Jan.) 1952. Schoenbach, E. B.; Bryer, M. S., and Long, P. H.: The Clinical Use of Polymyxin, Ann. New York Acad. Sc. **51**:987-997 (June 22) 1949.

5. Florestano, H. J., and Bahler, M. E.: Antifungal Properties of the Polymyxins, Proc. Soc. Exper. Biol. & Med. **79**:141-143 (Jan.) 1952.

6. Miller, J. L.; Slatkin, M. H., and Johnson, B. A.: Evaluation of Bacitracin in Local Treatment of Pyogenic Infections, Arch. Dermat. & Syph. **60**:106-120 (July) 1949.

The purpose of this investigation was to study such a preparation, namely Polysporin,[7] which contains 10,000 units of polymyxin B and 500 units of bacitracin per gram in a special low-melting petrolatum base, in which the drugs are very stable. That this combination of antibiotics is effective and has a low index of allergenicity and sensitization is indicated by the report on 147 patients treated with it in a water-soluble base by Gastineau and Florestano.[8]

EXPERIMENTAL

The ointment was used for the treatment of a variety of infected primary and secondary dermatoses in 429 patients. With 65 patients it was used prophylactically

TABLE 1.—*Patients Treated with Bacitracin-Polymyxin Ointment*

Diagnosis	No. of Patients	Condition			Comment
		Marked Improvement*	Improved†	Same	Worse	
Helix chronicus nodularis	3	..	..	3	..	
Otitis externa	5	1	2	2	..	
Pustules	10	1	8	1	..	
Infectious eczematoid dermatitis	83	13	60	9	1	Irritation, 1 patient; sensitive to bacitracin
Folliculitis	7	..	4	3	..	
Herpes simplex	6	..	5	..	1	One patient sensitive to white petrolatum
Impetigo	29	16	8	3	2	
Secondary pyogenic infections	88	22	61	5	..	Irritation, 1 patient; sensitive to bacitracin
Blepharitis marginalis	18	3	12	2	1	
Conjunctivitis	2	2	..	..	..	
Hidradenitis suppurativa	3	1	1	1	..	
Granuloma (nonspecific)	2	..	1	1	..	
Acne varioliformis	1	..	..	1	..	
Perlèche	2	..	1	1	..	
Fissures	36	7	29	..	..	
Prophylaxis‡	65	..	..	..	..	
Stasis ulcers	10	3	6	..	1	Irritation, 1 patient
Burns	7	6	1	..	..	
Furuncles	9	1	8	..	..	
Infected sebaceous cysts	3	..	3	..	..	
Pityriasis alba	1	..	1	..	..	
Paronychia	1	..	1	..	..	
Kerion	2	..	2	..	..	
Seborrheic dermatitis	1	..	..	1	..	
Ecthyma	4	3	1	..	..	
Sycosis	10	3	5	2	..	
Miscellaneous: x-ray burn, acne keloids, cheilitis, pyoderma gangrenosum, etc.	11	1	7	3	..	
Secondarily infected atopic dermatitis	7	4	3	..	..	
Total	429					

* Marked improvement, infection clear in less than one week.
† Improvement, infection clear or better in two to three weeks.
‡ Ointment used to prevent infection in patients treated with physical agents, such as irradiation, freezing, or fulguration.

to prevent infections after various procedures, such as fulguration, irradiation, and cryotherapy. One particular patient, with a stasis ulcer, who had a definite Pseudomonas infection both clinically and bacteriologically, did very well with this preparation. Although the basic condition, the ulcer, remained, the secondary infection cleared completely in the short period of about two weeks. The results and observations on these patients are tabulated in Table 1. Of the patients, 230, or 87% of the

7. Furnished by Burroughs Wellcome & Company, Inc.

8. Gastineau, F. M., and Florestano, H. J.: Clinical Experience with "Polycin," a Polymyxin-Bacitracin Ointment, A. M. A. Arch. Dermat. & Syph. **66**:70-79 (July) 1952.

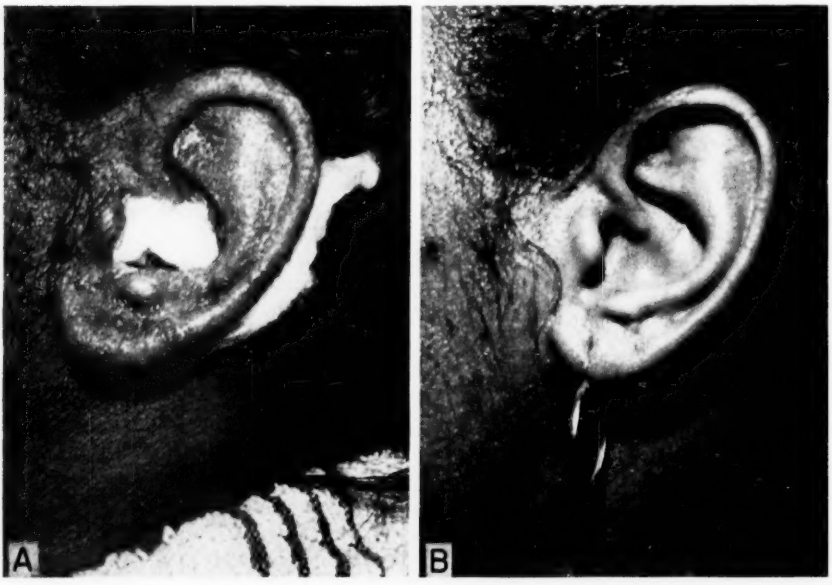

Fig. 1.—Infected seborrheic dermatitis before (*A*) and after (*B*) treatment for seven days.

Fig. 2.—Infected atopic dermatitis before (*A*) and after (*B*) treatment for two days.

group treated with the ointment for various dermatoses (excluding 65 given prophylactic treatment), were either markedly or moderately improved. This figure does not completely reflect the results, since there were included in this series a number of patients for whom we cannot definitely attribute the etiology to bacterial infection.

Figure 1 shows the results of therapy in a patient with secondarily infected seborrheic dermatitis. Figure 2 presents the results in a patient who had secondarily infected atopic dermatitis.

BACTERIOLOGY

Material for culture was taken in 78 instances and in 14 was sterile. All material was taken on swabs which were incubated overnight in heart-brain infusion (Difco) and then subcultured on blood agar plates. Hemolytic Staphylococcus aureus was found most frequently, 46 times; Pseudomonas, 5 times; other Gram-negative bacteria, 9 times, and miscellaneous organisms, 4 times. No tests for gelatin liquefaction or coagulase activity were done in the case of staphylococci, since we had found little correlation between the biologic activities in vitro and the clinical results in previous studies.[9]

TABLE 2.—*Sensitivity Studies with Strains Isolated from Skin Lesions*

Concentration (in Units) per Cc. of Medium		No. of Strains Inhibited		
Polymyxin B	Bacitracin	Hemolytic Staph. aureus	Ps. aeruginosa	Escherichia coli
0.09	0.007	0	0	0
0.19	0.015	1	1	0
0.38	0.031	0	0	0
0.77	0.062	0	0	0
1.55	0.125	2	1	2
3.1	0.25	5	0	0
6.2	0.5	10	2	2
12.5	1.0	20*	1	1

* Eight strains of Staphylococcus were not inhibited at this concentration.

The sensitivity tests were made in heart-brain infusion; the cultures were incubated for 18 hours at 37 C. For the routine sensitivity studies, the first tube was set up containing 12.5 units of polymyxin B and 1 unit of bacitracin per cubic centimeter. Serial dilutions were then made with each successive tube containing half the concentration of the previous tube. The results of these tests are shown in Table 2. Although eight strains of hemolytic Staph. aureus were not inhibited by bacitracin at a concentration of 1 unit per cubic centimeter, this is rather a severe test, since the minimal inhibiting concentration of this antibiotic for hemolytic Staph. aureus is believed to be in the range of 2 units per cubic centimeter or more.

In view of the great variability of the organisms, 13 cultures of Pseudomonas organisms recently isolated from patients (6 from urinary infections and 7 from skin lesions) were separately tested with polymyxin B and bacitracin and the majority also with the mixture of the drugs (Table 3).

It is obvious from our results that Pseudomonas in practically all cases shows considerable sensitivity to polymyxin B, and in one case an increase of sensitivity

9. Kile, R. L.; Rockwell, E. M., and Schwarz, J.: Use of Neomycin in Dermatology, J. A. M. A. **148**:339-343 (Feb. 2) 1952.

TABLE 3.—*Sensitivity Studies with Ps. Aeruginosa Cultures**

Strain No.	Concentration per Cc. of Medium (in Units): Polymyxin B 25	12.5	6.2	3.1	1.5	Bacitracin 1.0	0.5	0.25	0.12	0.06	Mixture of Polymyxin B and Bacitracin 25	12.5	6.2	3.1	1.5
											1	0.5	0.25	0.12	0.06
1	—	—	—	+	+	+	+	+	+	+	..	..	..	..	..
2	—	—	—	—	—	+	+	+	+	+	..	..	..	..	..
3	—	—	—	—	—	+	+	+	+	+	..	..	..	..	..
4	—	—	—	—	+	+	+	+	+	+	..	..	..	..	..
5	—	—	—	—	—	+	+	+	+	+	..	..	..	..	..
6	—	—	—	—	—	+	+	+	+	+	—	—	—	—	—
7	+	+	+	+	+	+	+	+	+	+	—	—	+	+	+
8	—	—	—	+	+	+	+	+	+	+	—	—	—	+	+
9	—	—	—	—	—	+	+	+	+	+	—	—	—	—	—
10	—	—	—	—	—	+	+	+	+	+	—	—	—	—	—
11	—	—	—	—	+	+	+	+	+	+	—	—	—	—	+
12	—	—	—	—	+	+	+	+	+	+	—	—	—	—	—
13	—	—	—	—	—	+	+	+	+	+	—	—	—	—	—

* Plus signs indicate growth; minus signs, inhibition.

TABLE 4.—*Studies of Sensitivity of C. Albicans to Polymyxin B**

Concentration of Polymyxin per Cc. of Medium (in Units)	250	125	62.5	31.2	15.6	7.8	3.9	1.95
Strain No.								
1	+	+	+	+	+	+	+	+
2	+	+	+	+	+	+	+	+
3	+	+	+	+	+	+	+	+
4	+	+	+	+	+	+	+	+
5	—	—	+	+	+	+	+	+
6	—	—	+	+	+	+	+	+
7	—	+	+	+	+	+	+	+
8	+	+	+	+	+	+	+	+
9	—	+	+	+	+	+	+	+
10	—	—	—	—	+	+	+	+

* Plus signs indicate growth; minus signs, inhibition.

TABLE 5.—*Correlation of Cultures with Clinical Results*

Culture	Marked Improvement	Improvement	Condition: Same	Condition: Worse	Total
Impetigo					
Staph.*	5	2	1	1	9
Infectious eczematoid dermatitis					
Staph.*	1	..	..	..	1
E. coli	1	1	..	..	2
Secondary pyogenic infections					
Staph.*	11	3	3	..	17
Pyocyan.†	4	1	..	..	5
E. coli	..	1	..	..	1
Bacillus proteus	..	2	1	..	3
Sycosis vulgaris					
Staph.*	..	3	..	..	3
Strep.‡	1	..	..	..	1
Folliculitis					
Staph.*	1	2	2	..	5
Miscellaneous					
Staph.*	2	..	1	..	3
Pyocyan.†	1	..	..	..	1
E. coli	..	1	..	..	1

* Hemolytic Staphylococcus aureus.
† Bacillus pyocyaneus.
‡ Hemolytic Streptococcus.

was obtained by the combination of polymyxin B with bacitracin.[10] Bacitracin alone did not inhibit Pseudomonas growth at the concentrations used in our experiment.

In view of recent publications [5] indicating the possibility that polymyxin B has antifungus properties, it was decided to evaluate the effect of this antibiotic on 10 recently isolated strains of C. albicans. Results of this study are given in Table 4. As expected, there was great variability among the strains. With the exception of Strain 10, which was partially inhibited, the others showed considerable resistance to the drug.

Table 5 presents the correlation between clinical results and cultural findings.

COMMENT

All of us are almost overwhelmed by the introduction of new antibiotics and various combinations for topical use on skin infections. The proper choice in a given case is often confusing. Cultures of and sensitivity tests on the offending organism are ideal to determine the most effective drug for the case under consideration, but these are often not practical in office practice.

Inasmuch as several antibiotics are available for topical use that are not in general use for systemic administration, it is probably wisest to favor them if at all possible. It was felt that the combination of an antibiotic effective against Gram-positive organisms (bacitracin) with one that is effective against Gram-negative organisms and especially Pseudomonas (polymyxin B) would be satisfactory. It was this type of preparation that was utilized in this study. Polymyxin B is considered the best available drug for Pseudomonas and certain other Gram-negative organisms.

Actually, in the concentrations of polymyxin employed, namely 10,000 units per gram, this antibiotic also shows activity against many Gram-positive organisms. In one series of sensitivity studies on hemolytic staphylococci, no growth was noted after a concentration of 500 units per gram was reached. This situation undoubtedly occurs with many Gram-positive strains.

Bacitracin, without apparent rationale, has been reported [11] as being effective in controlling chondrodermatitis nodularis chronica helicis. However, in the cases observed by us for several months, this was not borne out. No effect was noted in the condition as to either the pain or the size of the lesion.

In most cases, blepharitis marginalis appeared to respond extremely well to the preparation under study. Of 18 cases, the course in 15 was favorably influenced. For many of the common pyogenic skin lesions due to Gram-positive organisms, the results appeared about the same as those with bacitracin ointment. The results tabulated were in relation to the response to therapy of the secondary infection rather than of the basic underlying condition. In a large series of cases, infectious eczematoid dermatitis responded well to the ointment.

A few cases of irritation were observed in this series. However, when the antibiotic was the offending agent, tests with the individual components proved the

10. Neter, E.; Kunz, E. H., and Morgan, E. D.: Synergistic Effects of Polymyxin B and Terramycin on Bacteria Encountered in Urinary Tract Infections, J. Urol. **67**:773-775 (May) 1952.

11. Nelson, L. M.: Chondrodermatitis Nodularis Chronica Helicis: Treatment with Bacitracin Ointment, A. M. A. Arch. Dermat. & Syph. **65**:356-357 (March) 1952.

irritation to be due to the bacitracin. No case of sensitivity to polymyxin B was seen in this series. One case of sensitivity to the petrolatum base was observed, but this was considered unusual. Actually, the incidence of irritation to the ointment was low, and the preparation was felt to be very satisfactory from this standpoint.

With the widespread use of many antibiotics—particularly penicillin—there is a possibility of overgrowth of Pseudomonas or Proteus organisms as well as fungi. That this occurs has been established, mostly in the pediatric literature.[12] This problem is almost entirely avoided by the use of polymyxin. Undoubtedly, many such Gram-negative skin infections have gone undiagnosed with the use of other antibiotics on varied skin infections. This phenomenon may have accounted for the lack of response to therapy in some skin ulcerations in the past.

SUMMARY

A series of 429 patients with a variety of dermatoses were observed after treatment with a polymyxin B-bacitracin ointment. Bacteriological studies were done on 78 cultures of material from the skin lesions treated.

Owing to the inclusion of polymyxin B, this ointment, as would be expected from its in vitro results, was found to be very effective against infections due to Ps. aeruginosa.

The ointment had no effect in the several cases of chondrodermatitis nodularis chronica helicis observed.

Polymyxin B was not found significantly effective in vitro against the strains of C. albicans tested.

The incidence of irritation and sensitization was low.

The results of this study were of a nature to warrant general use of this preparation therapeutically for primary and secondary infections and prophylactically after procedures such as fulguration, irradiation, and cryotherapy.

12. Schaffer, A. J., and Oppenheimer, E. H.: Pseudomonas (Pyocyaneus) Infections of the Gastro-Intestinal Tract in Infants and Children, South. M. J. **41**:460-467 (May) 1948. Walker, S. H.: Polymyxin B in Pseudomonas and Proteus Enteritis, J. Pediat. **41**:176-181 (Aug.) 1952. Geppert, L. J.; Baker, H. J.; Copple, B. I., and Pulaski, E. J.: Pseudomonas Infections in Infants and Children, J. Pediat. **41**:555-561 (Nov.) 1952.

TYROTRACE IN TOPICAL THERAPY

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THE INTRODUCTION of a number of clinically effective antibiotics within the past few years has inevitably led to their use in combination, in the hope either of obtaining a higher percentage of favorable responses or of shortening the time necessary to eradicate the infection. Laboratory experiments have shown that combinations of antibiotics in vitro may give four types of results, namely, synergistic, additive, antagonistic, or indifferent.

The evidence for the synergistic action of certain antibiotics both in vitro and in vivo is well established. Combinations of the so-called bactericidal antibiotics, i. e., penicillin, bacitracin, and streptomycin, in doses individually far from adequate may produce an antibacterial effect greatly in excess of what could be expected on a purely additive basis. Eagle and co-workers [1] have shown that penicillin and bacitracin in vivo as well as in vitro have a remarkable synergistic action on the spirochete of rabbit syphilis. It was found that $\frac{1}{40}$ $C.D._{50}$ of penicillin alone and $\frac{1}{7}$ $C.D._{50}$ of bacitracin alone were curative if the two antibiotics were administered together. Johnson and Meleney [2] have shown that in vitro one-fifth of the minimal inhibitory concentration of penicillin plus one-fifth of the minimal inhibitory concentration of bacitracin will result in a killing time of four hours for 99.9% of certain strains of coagulase-positive Staphylococcus aureus (Micrococcus pyogenes, var. aureus). They found that the majority of such micrococcal strains were susceptible to this synergistic action regardless of whether the individual strains could be considered susceptible or resistant to one or both antibiotics. In their experience the synergistic action of these two antibiotics on streptococci was more strain specific. With certain strains the action was additive only. Clinically there is ample evidence that a combination of penicillin and bacitracin has given excellent results in osteomyelitis and acute and subacute endocarditis when penicillin alone has failed, even with doses as high as 12,000,000 units a day. Penicillin

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1. Eagle, H., and Fleischman, R.: Therapeutic Activity of Bacitracin in Rabbit Syphilis, and Its Synergistic Action with Penicillin: Preliminary Report, Proc. Soc. Exper. Biol. & Med. **68**:415, 1948.

2. Johnson, B. A., and Meleney, F. L.: Studies on the Synergism Between Bacitracin and Penicillin: Correlation of in Vivo with in Vitro Results, Ann. New York Acad. Sc. **53**:42, 1950.

and streptomycin have also given good results in the treatment of subacute endocarditis after there has been a poor clinical response to the administration of each of the antibiotics separately. Spicer [3] points out that in vitro, even in the case of strains very susceptible to the action of the so-called bactericidal antibiotics, there is a residue of viable organisms. When the proper combination of antibiotics was used, the cultures could be sterilized, i. e., all bacteria killed. However, Spicer also emphasizes that this observation must not be interpreted as a license for indiscriminate combination of antibiotics, because in some instances in which a strain was moderately or completely resistant to one of the antibiotics, a stimulation of growth occurred in the presence of the two drugs. For this reason it is necessary to determine the in vitro susceptibilities to combinations of antibiotics for the strain or strains recovered from an infection before or as soon as possible after chemotherapy is instituted.

It is only within the last two years that the possibility of antibiotics' exerting an antagonistic action upon each other has received due attention. Although some of the evidence presented seems rather tenuous, there is no doubt that under certain conditions the antibiotics which have a primarily bacteriostatic action, i. e., chlortetracycline (aureomycin), oxytetracycline (Terramycin), and chloramphenicol, can interfere with the efficacy of penicillin and streptomycin. Jawetz and co-workers [4] found that such antagonistic action could be demonstrated on Gram-positive (test strains: streptococci) and Gram-negative (test strains: Klebsiella) bacteria. In vivo they found that if chloramphenicol was given before or with a minimal curative dose of penicillin, the mortality from streptococcal infections in mice could be as high as 45 to 55%. If the penicillin was administered an hour or two before the chloramphenicol or in large amounts, there was little or no antagonism. Clinical proof of the existence of antagonism between penicillin and the broad-spectrum antibiotics is given in the report of Lepper and Dowling,[5] who found that of a group of 43 patients with pneumococcal menigitis treated with penicillin alone, only 30% died. When they treated 14 patients with a combination of chlortetracycline and penicillin, 79% died. The authors state that the two series were comparable as to type of patient and severity and duration of disease before treatment. Jawetz and his associates [6] have also reported the in vitro finding of antagonism when streptomycin was used with chlortetracycline, oxytetracycline, or chloramphenicol. The antagonism was present only when the organisms were susceptible to streptomycin. When the bacteria were resistant to streptomycin, a combination of the two antibiotics resulted in a synergistic action. These authors were able to demonstrate that a combination of streptomycin and oxytetracycline was bactericidal in vitro for a strain of Staphy-

3. Spicer, S.: Bacteriologic Studies of the Newer Antibiotics: Effect of Combined Drugs on Microorganisms, J. Lab. & Clin. Med. **36**:183, 1950.

4. Jawetz, E.; Gunnison, J. B.; Speck, R. S., and Coleman, V. R.: Studies on Antibiotic Synergism and Antagonism: The Interference of Chloramphenicol with the Action of Penicillin, A. M. A. Arch. Int. Med. **87**:349, 1951.

5. Lepper, M. H., and Dowling, H. F.: Treatment of Pneumococcic Meningitis with Penicillin Compared with Penicillin plus Aureomycin: Studies Including Observations on an Apparent Antagonism Between Penicillin and Aureomycin, A. M. A. Arch. Int. Med. **88**:489, 1951.

6. Jawetz, E.; Gunnison, J. B., and Speck, R. S.: Studies of Antibiotic Synergism and Antagonism: The Interference of Aureomycin, Chloramphenicol and Terramycin with the Action of Streptomycin, Am. J. M. Sc. **222**:404, 1951.

lococcus albus when neither one used alone was effective. This strain was isolated from the blood of a patient with bacterial endocarditis. The simultaneous use of these two antibiotics resulted in a cure. In one instance in which the organisms were resistant to oxytetracycline, no interference with the action of streptomycin was found.

Satisfactory explanation of the synergistic or antagonistic action on bacteria of combinations of antibiotics awaits a more complete knowledge of the intricacies of the mode of action of the several antibiotics on the different species of bacteria. An alteration in the cellular structure or metabolic processes of the bacterial cell by one drug may make it more or less susceptible to the mode of action of a second drug. In the case of synergistic action it is possible that the blocking of metabolic pathways may hasten the death of the cell either by hitting two different pathways or blocking the use of an alternate metabolic pathway that has enabled the bacterial cell to resist the action of one of the drugs. It is likewise not possible with the facts now available to explain the antagonistic action of one antibiotic or another. The combination of the two antibiotics could conceivably result in the formation of a new compound, antibiotically inactive. There is, however, no evidence that such formation occurs with penicillin or streptomycin and chlortetracycline, oxytetracycline, or chloroamphenicol. It is well to remember, however, that bacitracin and chlortetracyline do combine to form a new compound, aureotracin, which retains the antibacterial properties of both parent drugs.[7]

It has long been recognized that substances which have a complete and immediate bacteriostatic action, such as helvolic acid, nullify the action of a drug, such as penicillin, which exerts its bactericidal effect upon bacteria at the time of cell multiplication. It may well be, therefore, that the bacteriostatic action of chlortetracycline, oxytetracycline, and chloramphenicol prevents under certain conditions the optimum action of penicillin.

During the past 11 years, our group [8] has studied the effectiveness and the sensitizing capacities of the sulfonamides, penicillin, bacitracin, dihydrostreptomycin, and oxytetracycline in the local therapy of pyogenic dermatoses. The results obtained show that the average time required to cure pyogenic infections remains the same for all practical purposes, no matter which of the antibiotics is used, provided that the bacterial flora is susceptible to the antibacterial action of the therapeutic agent used. Therefore, in selection of a drug for therapy the sensitizing capacity of the individual drugs is of primary importance, and the drug of choice is the one that elicits the lowest percentage of allergenic reactions.

The present study was undertaken to determine whether a combination of antibiotics would give results superior to those we had obtained previously by the use of antibiotics singly. A combination of tyrothricin with bacitracin was chosen, since both antibiotics had given good results when used singly and both have low sensi-

7. Welch, H., and Lewis, C. N.: Antibiotic Therapy, Washington, D. C., Arundel Press, Inc., 1951.

8. (*a*) Miller, J. L.: Use of Sulfanilamide and Its Derivatives in Ointment Form: Local Treatment of Cutaneous Diseases, Arch. Dermat. & Syph. **46**:379, 1942. (*b*) Miller, J. L.; Rodriquez, S. S., and Domonkos, A. N.: Evaluation of Penicillin in Topical Therapy, New York J. Med. **47**:2316, 1947. (*c*) Miller, J. L.; Slatkin, M. H., and Johnson, B. A.: Evaluation of Bacitracin in Local Treatment of Pyogenic Infections, Arch. Dermat. & Syph. **60**:106, 1949. (*d*) Miller, J. L.; Slatkin, M. H.; Wechsler, H. L., and Johnson, B. A.: Dihydrostreptomycin in Topical Therapy, Arch. Dermat. & Syph. **61**:648, 1950.

tizing capacities. Tyrothricin has the advantage that its use is restricted to local application. Whenever possible we prefer to use a drug for local therapy whose systemic use is precluded or limited, thus avoiding the risk of sensitizing a patient to an antibiotic that may at some future time be needed for parenteral use. Tyrothricin has the disadvantage of having poor or no penetrative powers and does not diffuse into surrounding tissues. The combination of tyrothricin with bacitracin does not widen the antibacterial spectrum of the drugs used singly. Tyrothricin is in itself a combination of two antibiotics, gramicidin and tyrocidine. Commercial tyrothricin contains approximately 20% gramicidin and 80% tyrocidine. Although tyrocidine has an active bactericidal action upon washed suspensions of Gram-positive bacteria and some Gram-negative organisms, it is inactive in the presence of blood or pus. In vivo, therefore, the antibacterial action of tyrothricin is almost wholly due to its gramicidin content. Gramicidin is an effective antibacterial agent in vitro and in vivo against the Gram-positive cocci, the clostridia, and Neisseria. Its spectrum therefore parallels that of bacitracin. However, the action of bacitracin is predominantly bactericidal, while that of gramicidin is primarily bacteriostatic. The combination of bacitracin and tyrothricin has been reported to have a synergistic action.[9] In a series of laboratory experiments we found evidence of synergistic action on streptococci and staphylococci in the absence of blood or serum. However, when blood or serum was added to the medium, the action was additive only. Details of these experiments will be reported elsewhere by one of us (B. J.). For simplicity the mixture of tyrothricin and bacitracin is called tyrotrace. There is no evidence that the combination of these two antibiotics forms a new chemical compound, but there is evidence, rather, that it remains a physical mixture.

PROCEDURE

All our patients were treated with an ointment containing 500 units of bacitracin and 500 γ of tyrothricin per gram of ointment base. The antibiotics were incorporated in a modified petrolatum base.

Patients were seen in the outpatient clinic. They were advised to apply wet compresses of saline solution twice a day for 10 minutes and then to apply the ointment. The necessity for removal of crusts before any medication is applied is obvious. For this purpose, wet compresses are preferable, usually of saline solution. Compresses remove crusts painlessly as well as effectively and do not irritate the skin, as soap and water may. A few patients were treated with the ointment base alone, or one extremity was treated with the base and the other extremity with tyrotrace.

Cultures were taken in all cases to determine the organisms present. Susceptibility of these organisms to bacitracin, penicillin, streptomycin, and oxytetracycline was tested routinely on blood agar plates by the filter-paper disc method. The results are given in Table 1. Sensitivities to penicillin, streptomycin, and oxytetracycline as well as to bacitracin were included to ascertain any increase in percentages of resistance to one or all antibiotics in comparison with those obtained in similar studies in previous years. There was no striking increase in resistance to any of the antibiotics by any species of bacteria. There was a slight decrease in resistance to penicillin on the part of the coagulase-positive staphylococci from 45% in 1950 to 34% in 1951-1952. This decrease, although small, was made more significant by the fact that in the series of staphylococcal infections treated in the surgical outpatient departments, the incidence of resistance fell from 43% in 1950 and 1951 to 31% in 1952. Since tyrothricin does not diffuse through blood agar, and therefore could not produce zones of inhibition of growth of susceptible bacteria, susceptibility or resistance to tyrothricin was determined by the dilution method in tubes of serum broth. It proved impossible to test all

9. Lubowe, I. I.: The Use of Bacitracin-Tyrothricin Ointment in the Treatment of the Pyogenic Dermatoses, New York J. Med. **51**:611, 1951.

strains isolated, but the susceptibility of a representative number of strains of each species was assayed. The results are given in Table 2. The range of susceptibilities shows that with the exception of two cases, in which the staphylococcal strains isolated were not inhibited by 50 γ per cubic centimeter of tyrothricin in serum broth, all the lesions in which the Gram-positive cocci were the causative organisms should have been amenable to local application of tyrothricin. No attempt was made to study systematically the development of resistance by the organisms to the antibiotics used, for previous studies had shown this development of resistance over the period during which these patients were treated to be of real significance only with streptomycin.

RESULTS

Of the 143 patients treated, 120 were adequately followed. Examination of Table 3 shows that of 25 adequately followed patients with impetigo contagiosa, 24

TABLE 1.—*Sensitivities of Strains of Bacteria Recovered from Pyogenic Dermatoses* (June, 1951, to September, 1952)*

Organism	No. of Strains	% Sensitive to			
		Penicillin	Bacitracin	Streptomycin	Oxytetracycline
Coagulase-positive staphylococci	104	66	97	98	88
Coagulase-negative staphylococci	12	58	83	60	20
Beta hemolytic streptococci†	26	85	100	37	92
Nonhemolytic streptococci	11	54	100	45	100
Coli-aerogenes group	11	..	..	72	68
Proteus	11	..	..	54	36
Pseudomonas	12	..	..	50	42

* Blood agar plate, filter-paper disc method.
† Beta hemolytic streptococci were not grouped.

TABLE 2.—*Sensitivities to Tyrothricin of Bacteria Recovered from Patients with Pyogenic Dermatoses* (June, 1951, to September, 1952)*

Organism	No. of Strains	Minimal Inhibitory Concentration, γ/Ml.			
		0.01-2	2.5-5	6-20	50
Coagulase-positive staphylococci	54	4	37	11	2
Coagulase-negative staphylococci	10	1	6	3	0
Beta hemolytic streptococci†	20	15	4	1	0
Nonhemolytic streptococci	10	3	5	2	0
Coli-aerogenes group	11	..	..	..	11
Proteus	10	..	..	..	10
Pseudomonas	9	..	..	..	9

* Dilution method in 10%-serum, beef-heart infusion broth.
† Beta hemolytic streptococci not grouped.

were cured in a median time of seven days. The treatment of one was listed as a failure. This failure occurred in a boy with localized bullous impetigo on the right knee. The original lesions healed in five days, but new lesions developed in the surrounding skin. These in turn healed in a few days, but new lesions again developed. The original cultures and repeat cultures of material from three new lesions all showed a hemolytic Staph. aureus sensitive to bacitracin and tyrothricin. Treatment was continued with tyrotrace for 40 days. One injection of penicillin did not influence the course of the infection. Sulfisoxazole (Gantrisin) by mouth was effective. This case should be classed as a failure of local therapy rather than failure of the specific antibiotics used, since some of the new lesions were distant from the sites of the original infection.

In six cases of ecthyma, the lesions cleared in a median time of 15 days, and all patients were cured. One patient required 33 days of treatment before all lesions were healed. The first cultures of material from the lesions on the arms and legs showed a beta hemolytic Streptococcus and a hemolytic Staph. aureus, both sensitive to bacitracin and tyrothricin. The lesions healed in 14 days but recurred one week later. Cultures of material from these new lesions revealed a hemolytic Streptococcus sensitive to bacitracin and tyrothricin and Escherichia coli resistant to bacitracin and tyrothricin. Use of tyrotrace was continued, and all lesions had healed after 33 days, with no further recurrences.

Of the 19 patients with infectious eczematoid dermatitis, 15 were cured in a median time of seven days. There were four failures. One of these failures occurred in a patient whose lesions have proved resistant for six months to many forms of therapy. Cultures showed a nonhemolytic Staphylococcus which was resistant to bacitracin and moderately sensitive to tyrothricin. One instance of acute reaction

TABLE 3.—*Results in Treatment of Primary Superficial Infections of the Skin with Tyrotrace Ointment*

Diagnosis	Total No. of Cases	No. of Cases Adequately Followed	No. of Cures	No. of Failures	No. of Reactions to Medication	Time Required for Cure, Days		
						Maximum	Minimum	Mean
Impetigo contagiosa	33	25	24	1	0	30	3	7
Ecthyma	7	6	6	0	0	33	4	15
Infectious eczematoid dermatitis	22	19	15	4	1	27	3	7
Folliculitis of the beard	8	6	2	4	0	35	10	—
Folliculitis elsewhere	9	5	4	1	0	21	4	12
Furunculosis	4	4	3	1	0	18	7	13
Vesiculopustular eruption of the hands	6	5	3	2	0	16	7	12
Otitis externa	3	3	1	2	0	14	..	..
Acne varioliformis	1	1	1	..	0	5	..	..
Paronychia	1	1	1	..	0	18	..	..
	94	75	60	15	1	..	..	..

to tyrotrace was encountered. A patch test to tyrotrace, done three weeks later, was negative. Cure of the patient was accomplished by intramuscular injection of penicillin.

Of the six patients with folliculitis of the beard, two were cured and the treatment of four failed. Duration of infection before this treatment was started seemed to be of no significance, since one patient who was cured had had the infection for one year, whereas in two whose treatment failed, the infection had been present only two weeks.

Of the five cases listed as instances of folliculitis elsewhere, cure occurred in four and failure in one. The patient who failed to respond had an atypical folliculitis, and culture material taken from the lesions showed no growth of any organisms.

The one failure listed under furunculosis occurred in an obese woman with a number of furuncles in intertriginous areas. She had resisted treatment with penicillin intramuscularly. Cultures of material from the lesion showed a Staph. aureus sensitive to bacitracin and tyrothricin and Bacillus subtilis. Failure of local therapy is not unexpected in the case of deep furuncles. There was a prompt response to sulfisoxazole.

Of the five patients with vesiculopustular eruptions of the hands, three were cured and two were not. Cultures of material from one whose treatment failed showed no growth, and the patient had a badly infected tooth. The other failure occurred in a patient in whom the lesions had been present for two years. Culture revealed a Staph. aureus which was bacitracin- and tyrothricin-sensitive. Following the use of tyrotrace there was initial improvement, with a subsequent relapse.

Of the three patients with otitis externa, the treatment of two failed and one patient was cured. The patient who was cured had had the infection for two years. Cultures showed a Staph. aureus, a hemolytic and a nonhemolytic Streptococcus and an Esch. coli. All the organisms were sensitive to bacitracin and tyrothricin except the Esch. coli. The response to tyrotrace was rapid and has been permanent to date. One patient who failed to respond had had the infection in her ears for two years. The original culture showed a Staph. aureus which was sensitive to bacitracin, streptomycin, and oxytetracycline but resistant to penicillin. Repeat cultures after

TABLE 4.—*Results of Treatment of Secondary Infection with Tyrotrace Ointment in Various Dermatoses*

Disease in Which Secondary Infection Appeared	Total No. of Cases	No of Cases Adequately Followed	No. of Cures	No. of Failures	No. of Reactions to Medication	Time Required for Cure, Days		
						Maximum	Minimum	Median
Allergic dermatitis	14	13	12	1	0	15	2	8
Contact dermatitis	14	12	12	0	0	28	3	7
Dermatophytosis	6	6	6	0	0	8	4	6
Herpes simplex	3	3	3	0	0	6	5	5
Neurodermatitis	1	1	1	0	0	5	..	..
Scabies	1	1	1	..	..	6	..	..
Herpes zoster	1	1	1	..	0	7	..	..
Pemphigus vulgaris	1	1	1	..	0	7	..	..
Pustular psoriasis	1	1	..	1	0	..	..	..
Dermatitis repens	1	1	..	1	0	..	..	..
Seborrheic dermatitis	1	1	..	1	0	..	..	..
Miscellaneous ulcers	5	4	2	2	0	28	7	..
	49	45	39	6	0	..	..	..

two weeks of tyrotrace treatment also showed a Staph. aureus, but it was resistant to all four of the antibiotics mentioned previously, although sensitive to neomycin. This difference in sensitivities would warrant the assumption this was a different strain from that orginally isolated, since there is no evidence for cross resistance developing between bacitracin and streptomycin or oxytetracycline. The use of neomycin gave temporary improvement, followed by relapse.

In Table 4 are listed the results of the treatment with tyrotrace in 45 adequately followed cases of various dermatoses with secondary infection. The secondary infection was cleared in 39 cases and failed to clear in 6. Three of the failures occurred in patients with pustular psoriasis, dermatitis repens, and seborrheic dermatitis, respectively. The treatment of one diabetic patient with an ulcer which showed Proteus on culture and that of one patient with sickle cell anemia and an ulcer which showed Proteus and Staph. aureus on culture are listed as failures, since secondary infection was still present after several weeks of treatment. The sixth failure was in a patient with allergic dermatitis who still showed evidence of secondary infection after 28 days of treatment.

COMMENT

As was to be anticipated, tyrotrace proved to be an effective agent in the local treatment of pyogenic infections of the skin. In the laboratory we found in vitro evidence for synergism between tyrothricin and bacitracin in the absence of blood or serum and of an additive action in the presence of these body fluids. There is no evidence that a new compound is formed.

No attempt was made to take advantage of the possible synergistic or additive action found in the laboratory, for more than adequate concentrations of each antibiotic were combined in the ointment. This study was begun with the hope that tyrotrace would be more effective than bacitracin alone. Analysis of our clinical results does not show any decided evidence for a superior effectiveness in this series of cases over similar series we have studied previously, using antibiotics singly. For example, for impetigo the median time of cure varied from five to eight days when we used dihydrostreptmoycin,[8d] bacitracin,[8c] penicillin,[8b] or the sulfonamides.[8a] With tyrotrace the median time of cure was seven days. Although we have cured many patients with impetigo in two or three days, the median time of cure of five to eight days probably represents an irreducible minimum in a statistically significant group. The over-all percentage of failure is approximately the same with tyrotrace as with other antibiotics. It is probable that pyogenic infections of the skin do not represent the type of disease in which this combination of antibiotics will show definitely superior results. The reason is that the important causative organisms found in cases of these infections are the Gram-positive pyogenic cocci and should respond to bacitracin or tyrothricin alone. The Gram-negative organisms which are encountered probably play an insignificant role with the exception of those found in otitis externa and media. In our experience the use of dihydrostreptomycin or oxytetracycline, to which many of these Gram-negative bacilli are susceptible, did not give a higher percentage of favorable results or a shortening of the median time of cure. It is possible that an improvement in results might follow a more careful selection of cases for local versus systemic therapy. It is also probable that results might be improved if patients could be treated daily in the clinic and advised adjunctive therapy be more closely followed.

The objection that the use of two antibiotics would increase the rate of sensitization did not materialize in this study. There was one instance of sensitization among 120 patients, which makes the rate of sensitization 0.85%. Even this one patient had a negative patch test to tyrotrace and was able to use it subsequently without reaction. Lubowe [9] found one instance of sensitization among the 50 patients he treated.

In conclusion, we feel that the combination of tyrothricin and bacitracin has proved an effective agent, with a sensitization rate of less than 1%.

CONCLUSIONS

Tyrotrace, a combination of tyrothricin and bacitracin, proved an effective agent in the local treatment of pyogenic infections of the skin.

The rate of sensitization of the patients was less than 1%.

The results obtained with the combination were not outstandingly superior to those obtained when bacitracin or other antibiotics were used singly.

Realization of the limitations of local therapy in certain cases might lead to improved results.

FLUORESCENCE OF MICROSPORUM AUDOUINI-INFECTED HAIR

II. Cultural Studies

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WE HAVE conducted a series of experiments to learn more of the nature of Microsporum audouini-infected hairs and the fluorescence produced by this fungus on exposure to the Wood light. In our previous experiments, studies were performed to determine the chemical behavior of the fluorescent substance and its chemical composition. In this portion of our investigation attempts were made to produce fluorescence on artificial media, to inhibit the growth of M. audouini by the addition of various substances to the media, and to determine the longevity of the fungus in infected hair.

CULTURAL STUDIES ON PRODUCTION OF FLUORESCENCE

A protein-free, vitamin- and mineral-enriched medium was used in all the experiments conducted in this portion of the study. The following formula was used in the preparation of the medium:

Dextrose (neutralized)	30 gm.
Potassium acid phosphate	1.5 gm.
Magnesium sulfate	0.5 gm.
Agar (purified)	18 gm.
Distilled water to make	1,000 cc.

To each liter of medium was added 1 cc. of sterile mineral solution containing:

Boric acid	5.7 mg.
Copper sulfate	18.6 mg.
Iron ammonium sulfate	173 mg.
Magnesium sulfate	0.1 mg.
Ammonium molybdenate	3.6 mg.
Zinc sulfate	79 mg.
Distilled water to make	100 cc.

This mixture was brought to pH 5.5 by adding 2 N sodium hydroxide. The following vitamins were also added to the medium after Seitz filtration:

Thiamine hydrochloride	400 γ per liter
Pyridoxine hydrochloride	400 γ per liter
Nicotinic acid	400 γ per liter
Calcium pantothenate	400 γ per liter
Riboflavin	400 γ per liter
Folic acid	400 γ per liter
Biotin	4 γ per liter
Inositol	20,000 γ per liter

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In an attempt to produce fluorescence on artificial media, the following amino acids, which are present in the keratin of human hair, were sterilized by Seitz filtration of their aqueous solutions and incorporated into the above media, 500 mg. per liter: arginine, phenylalanine, tryptophan, histidine, aminoacetic acid, tyrosine, lysine, cystine. Two tubes containing the medium plus each of the amino acids and two tubes containing a combination of all eight were inoculated with a stock culture of M. audouini, and another similar set of tubes were inoculated with M. audouini-infected hairs. These were incubated at room temperature for eight weeks. Typical colonies of M. audouini grew on each preparation, but weekly examinations of each tube under the Wood light were negative for the characteristic fluorescence produced by infected hair.

Other substances possibly concerned with the production of fluorescence of M. audouini-infected hair were also incorporated into separate tubes of the medium in the following concentrations:

Ammonium nitrate	500 mg. per liter
Nucleic acid	500 mg. per liter
Melanin	20 mg. per liter

As in previous experiments, tubes containing each of these substances were inoculated with stock cultures of M. audouini and M. audouini-infected hair. The characteristic greenish fluorescence of infected hair was not produced by any of the growths, but colonies in the tubes containing melanin did produce a dull gray appearance when exposed to the Wood light.

INHIBITION OF MICROSPORUM AUDOUINI GROWTH ON ARTIFICIAL MEDIA

In an attempt to inhibit growth on artificial media the following substances were incorporated into separate tubes of the same medium used in the previous experiments:

Amniotin (commercial)	100 mg. per liter
Testosterone (commercial)	5,000 mg. per liter
Human sebum (from a sebaceous cyst)	2,000 mg. per liter
Protoporphyrin	500 mg. per liter
Hematoporphyrin	1,000 mg. per liter
Tin porphyrin	900 mg. per liter

Casein hydrolysate, 20 cc. per liter, was added to the media in this series of experiments as a source of protein, and a control with this substance was also included. Separate sets of these prepared tubes were inoculated with stock cultures of M. audouini and M. audouini-infected hair, and incubated at room temperature. Characteristic colonies of M. audouini grew in all the tubes except those in which the various porphyrins had been incorporated. These in vitro experiments indicated that the various porphyrins, when incorporated in the media in the concentrations previously described, will inhibit the growth of M. audouini.

LONGEVITY OF MICROSPORUM AUDOUINI IN EXTRACTED HAIR

Farley [1] demonstrated that hair infected with M. audouini produced a growth on culture media 420 days after removal from the scalp. These results were con-

1. Farley, D. L.: Viability of Ringworm Fungi in Dry Cutaneous Material, Arch. Dermat. & Syph. **3**:759, 1921.

firmed by Robinson.[2] Glass [3] reported that hair infected with this fungus produced a growth on Sabouraud's medium 460 days after removal from the scalp, but no growth was obtained after 479 days.

During the course of earlier experiments,[2] infected hair was stored in rubber-stoppered glass tubes. Tubes labeled Jan. 3 and Jan. 5, 1947, contained hair which still possessed the characteristic greenish fluorescence when examined under the Wood light on Feb. 27, 1952. However, repeated attempts to produce a growth on Sabouraud's medium with this fluorescent hair were nonproductive. These results indicate that the production of greenish fluorescence in hair when examined under the Wood light does not imply that a viable fungus is present, but it does suggest that a chemical compound is produced by the invasion of Microsporum and that the product does not undergo rapid spontaneous degeneration. The fact that when infected hair is removed from the scalp the fungus eventually loses viability suggests that the nutritive value of the hair is gradually exhausted by the fungus, and when this occurs the organism loses its power to reproduce on artificial media.

SUMMARY AND CONCLUSIONS

Attempts to produce fluorescent material on artificial media failed. Various combinations of the amino acids found in keratin were added to artificial media and the tubes were inoculated with stock cultures of M. audouini and infected hair, but fluorescence was not produced. Growth was not inhibited on artificial media by the addition of testosterone, amniotin, and human sebum. The addition of protoporphyrin, hematoporphyrin, and tin porphyrin definitely inhibited growth of M. audouini on culture media.

The production of fluorescence by infected hair when exposed to the Wood light does not imply that a viable fungus is present. When infected hair is removed from the scalp, viability of the fungus will eventually be lost, but fluorescence will be retained. Infected hair used in this portion of the study was five years old and retained fluorescence, but the fungus had lost its viability. The fungus in infected hair will remain viable for from 420 to 460 days after removal from the scalp.

2. Robinson, H. M., Jr.: In Vitro Studies of Microsporon Audouini Infection of the Hair, Arch. Dermat. & Syph. **57**:991, 1948.

3. Glass, F.: Viability of Fungus in Hairs from Patients with Tinea Capitis: Microsporon Audouini, Arch. Dermat. & Syph. **57**:122, 1948.

DYSIDROSIS (POMPHOLYX)

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DYSIDROSIS was first distinguished as a clinical entity by Tilbury Fox in 1873. During that year two succinct reports [1] from his pen clearly described to both European and American clinicians his views on the etiology, pathogenesis, and clinical picture of this eruption, which was previously considered a part of the great eczema group. Fox felt unequivocally that one could identify a group of acute noninflammatory vesicular eruptions of the palms which arose simply on the basis of poral occlusion and consequent sweat retention. These views on etiology led to his choice of a name, dysidrosis, i. e., difficult sweating.

He stated that dysidrosis bore the same relation to the sweat gland as acne did to the sebaceous gland. His etiologic concept was sound and attractive, although initially supported solely by deductive reasoning. Certainly there was a distinctive group of purely vesicular hand eruptions which could be distinguished from the common inflammatory eczematous eruptions.

Three years later the famed surgeon Jonathan Hutchinson,[2] apparently unaware of Fox's previous publications, described the same condition under the name of cheiropompholyx, i. e., a vesicular eruption of the hands. He ascribed no etiologic role to the sweat gland. His article immediately launched a great dermatologic debate, which has been waged in 150 publications during the past three-quarters of a century.

The present communication attempts to describe the current status and significance of dysidrosis, and also reviews some of the special studies done by my colleagues and me to delineate the role of the sweat gland in dysidrosis.

CLINICAL DESCRIPTION

For the purpose of this report dysidrosis (pompholyx) may be defined as an acute, recurrent, noninflammatory vesicular eruption strictly limited to the palms and/or soles. The process is not seen elsewhere except as an extension onto the lateral surfaces of the fingers or toes. It occurs in both sexes and may be seen most commonly in adults. The primary lesion is a vesicle which is clear, deep-seated, and nonerythematous (Fig. 1). It is also sterile. The vesicles may be pruritic and at times may enlarge or coalesce to form bullae. The classic form of dysidrosis is a

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1. Fox, T.: On Dysidrosis, Am. J. Syph. & Dermat. **4**:1, 1873; Dysidrosis: An Undescribed Eruption, Brit. M. J. **2**:365, 1873.

2. Hutchinson, J.: Cheiro-Pompholyx: Notes of a Clinical Lecture, Lancet **1**:630, 1876.

symmetrical and diffuse eruption. Clinically, however, patchy or localized areas of noninflammatory vesiculation of the palms and soles cannot be excluded. Vesicular eruptions of the dorsum of the hand or foot, as well as patchy eczematoid eruptions of the hand, are not included. Vesicular eruptions of the palm and sole which, although clinically and histologically identical with dysidrosis, are associated with widespread cutaneous changes are also excluded. In these disturbances, the dysidrosiform eruption of the palms and soles is simply a part of the general pattern.

The normal course of dysidrosis is one of sudden onset and rapid evolution, followed by complete spontaneous involution in two to three weeks. Scaling marks

Fig. 1.—Severe dysidrosis of palm. Note confluence of vesicles and sharp limitation of eruption to palmar skin. Ordinarily, dysidrosis consists of small sago-grain vesicles which are difficult to reproduce photographically.

the terminal phase. The vesicles do not rupture and exude serum spontaneously. Involution is the result of epidermal resorption of vesicular fluid.

Repeated attacks occur as a rule, seasonal exacerbations being common in summer. Hyperhidrosis of the palms and soles is the usual concomitant of dysidrosis.

It is worthy of note that dysidrosis frequently is prey to secondary changes or complications. The lesions may become secondarily infected or, owing to topical medication, contact dermatitis and secondary eczematization may ensue. As a result many patients with dysidrosis may first be seen by the physician in a stage in which the underlying disease is no longer discernible.

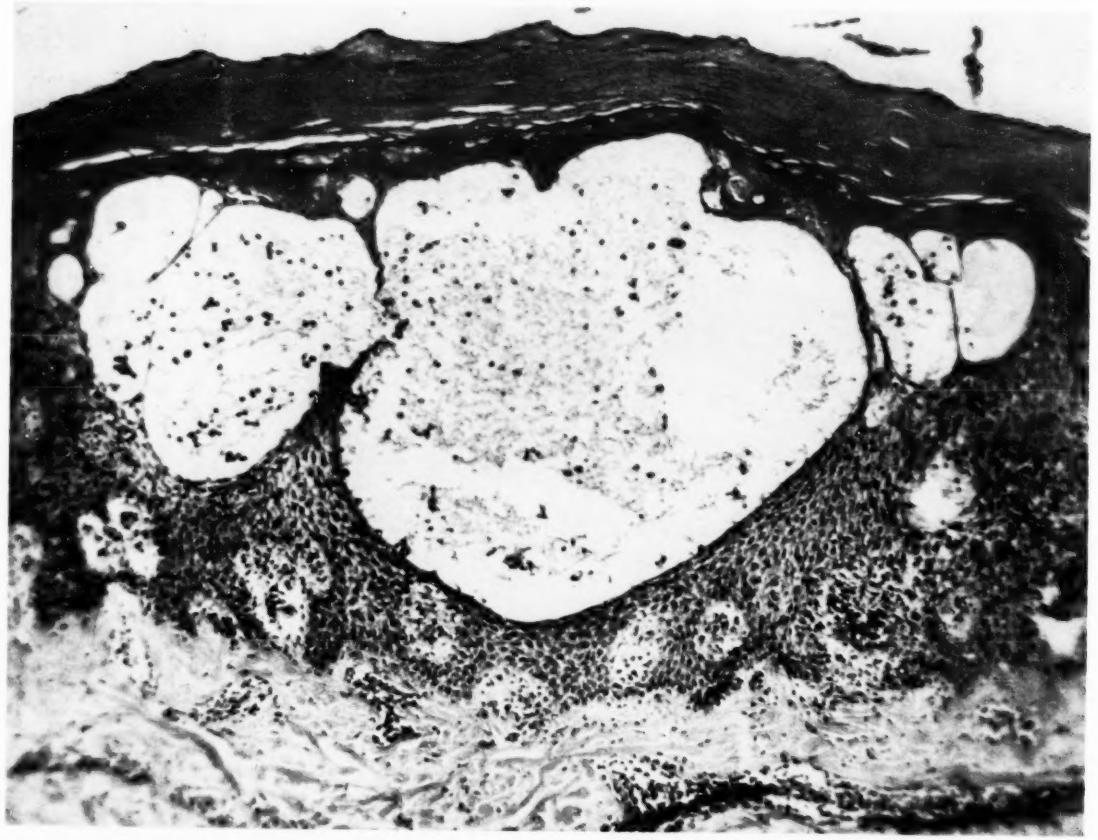

Fig. 2.—Histopathological findings in dysidrosis. Biopsy specimen of a palmar lesion seen in Figure 1. Note superficial epidermal vesiculation and absence of marked changes in corium.

HISTOPATHOLOGY

Fundamentally dysidrosis manifests itself as a superficial vesicle (Fig. 2) in the epidermis. There is no significant inflammatory change to be seen in the corium. The most recent careful histologic studies prove the vesicle to be independent of the sweat duct.[3]

It is interesting to correlate the superficial histologic location of the vesicles with the clinical appearance, which is that of a deep-seated sago-grain vesicle. Apparently the thick stratum corneum is responsible for this clinical impression and also may account for the fact that rupture does not occur.

ETIOLOGY

Tilbury Fox's claim that the vesicles of dysidrosis contain trapped sweat has never been satisfactorily confirmed, although brilliant protagonists have championed this hypothesis.

Our experimental studies on dysidrosis have aimed at elucidating the potential significance of the sweat gland in dysidrosis. Uniformly they have indicated that apparently the sweat gland is not primarily responsible for dysidrosis. The results of these studies may be summarized as follows:

1. *Anatomical.*—Serial sections of biopsy specimens from two patients presenting typical dysidrosis failed to show a connection between the dysidrotic vesicles and the sweat ducts.

2. *Physiological.*—In collaboration with Dr. Sheldon Goldstone, 10 patients with bilaterally symmetrical palmar dysidrosis were given 1/120 grain (0.50 mg.) of atropine sulfate intra-arterially in one arm. This caused unilateral arrest of palmar sweating for several hours. In this period of local anidrosis no change could be seen in vesicle size or appearance on either side. In patients with lesions known to be due to sweat retention, similar blocking of sweat gland activity results in appreciable involution of the lesions in several hours.

3. *Chemical.*—Analysis of fluid from beginning vesicles of 10 patients who had palmar dysidrosis of unknown cause revealed the presence of protein (spot test using α-nitroso-β-napthol)[4] in all specimens. This observation favors an epidermal origin for the vesicles rather than sweat retention, since sweat is protein free.

4. *Experimental.*—An attempt to produce dysidrosis experimentally by inducing poral occlusion of the sweat glands of the soles was unsuccessful. Sweat retention anidrosis of the soles was produced in four hyperhidrotic patients by means of daily application of an aluminum chloride powder. No dysidrotic vesicles were seen, although after 10 days thick layers of stratum corneum peeled, possibly because of the mechanodissections of the layer by the pressure of trapped sweat.

Direct observation of the vesicles of dysidrosis was done with a stereoscopic dissecting microscope (10 to 30 power). Many of the vesicles appeared as local areas of anhidrosis. However, at times, sweat could be seen to appear in pores at the summit of the vesicles. This observation is compatible with histologic observations of an intact duct occasionally coursing through the dysidrotic vesicle.[3a] In these instances it would appear that the sweat retention theory of origin of the vesicles would be inadequate. Although primary sweat retention can be reasonably well ruled out as a cause of dysidrosis, secondary sweat retention may occur, just as it

3. (*a*) Devine, D. C.: Observations on the Relationship of the Sweat Ducts to Pompholyx Vesicles, Brit. J. Dermat. **64**:393, 1952. (*b*) Wilson, H., and Thackeray, A. C.: Sweat Ducts and the Pompholyx Vesicle, Brit. J. Dermat. **64**:402, 1952.

4. Feigl, F.: Qualitative Analysis by Spot Tests, Ed. 3, New York, Elsevier Press, Inc., 1947.

does in numerous dermatidides, e. g., contact dermatitis. Such secondary sweat retention would lead to an intensification of dysidrosis, and the elimination of this factor might account for the improvement observers have reported as a result of using atropine or atropine-like preparations.[5] Lobitz,[6] in this respect, made a significant observation, that unilateral sympathectomy resulted in considerable improvement in a patient who had a recurrent dysidrosiform eruption of the hands. During recurrent attacks the sympathectomized anidrotic side exhibited tiny vesicles, in contrast to the control side, which was hyperhidrotic. One interpretation of the results of Lobitz' study would be that the secondary sweat factor had been eliminated by sympathectomy, with a consequent reduction in the size of the dysidrotic vesicle. Other interpretations are possible.

Fig. 3.—Etiologic factors known to be capable of inducing dysidrosis reaction pattern.

Clinical observations incline my associates and me to the view that dysidrosis is a nonspecific reaction pattern of palmar and plantar skin. The various causes of dysidrosis have been schematically portrayed in Figure 3. The cause is not known in the majority of cases. Nevertheless there are at least four etiologic agents which may be discerned from time to time. The first of these is the one stressed by Hutchinson and noted by Fox, viz., the psychosomatic factor. Numerous patients relate histories of repeated bouts of dysidrosis, each attack precipitated by psychologic stresses. Wittkower [7] has reported that emotional factors were etiologically operative in 40 of 50 cases of dysidrosis.

5. (*a*) Brown, C. S., and Sandler, I. L.: Effective Application of Banthine in Dermatology, A. M. A. Arch. Dermat. & Syph. **64**:431, 1951. (*b*) Wulf and Suhr: Dyshidrosisbehandlung mit Atropin, Arch. Dermat. u. Syph. **191**:492, 1950.

6. Lobitz, W. C., Jr.: Personal communication to the author.

7. Wittkower, E.: The Psychological Aspects of Skin Disease, Bull. Menninger Clin. **11**:148, 1947.

Primary fungous infection with a dermatophyte is another cause of dysidrosis. This cause was not widely recognized until after the turn of the century and at first was erroneously felt to account for all cases of dysidrosis.

Later, it was shown conclusively that in patients presenting an active inflammatory fungous infection of the feet, dysidrosis of the palms (and soles) could arise on the basis of an allergic state. This was described as an id reaction. Again, a wave of enthusiasm prompted many to maintain that in all cases dysidrosis occurred on the basis of a fungous infection and/or an allergic id phenomenon.

Aside from these four rather well-grounded etiologic factors, myriads of supposedly responsible agents have been proposed. These include bacterial sensitivity, foods, infected sinuses, neurologic changes, autonomic nervous system disturbance, hormones, and spirochetes. Epidermal sensitization has also been named as a cause. However, these views have been honored by only the occasional observer and have not met with popular favor. The need for further study of the etiologic background of dysidrosis is obvious.

The term dysidrosis has historical priority over pompholyx and has been accordingly retained, although it is a misnomer. It may be necessary to amplify the nosologic reason for retaining the entity dysidrosis.

Treatment can be most satisfactorily instituted if the cause of dysidrosis is known. Psychotherapy, appropriate antifungal measures, or elimination of drugs each may have specific merit. In any event, proper topical medication minimizes the opportunity for secondary infection and contact eczematization. Usually compresses are soothing in the early stages of the disease; later the use of an emollient cream is of value. If secondary infection has occurred, local or systemic antibiotic therapy may be appropriate. Penicillin generally is avoided, in view of its capacity to induce dysidrosis.

Sedatives may be employed to allay tension. Atropine has been favored by many because in effective doses it greatly reduces the hyperidrosis of the palms and soles. The latest contribution on this aspect of therapy has been by Wulf and Suhr.[5b] Atropine could be anticipated to be of value in the treatment of patients in whom secondary sweat retention might be prominent. A large group of synthetic atropine-like compounds (diphenmethanyl methylsulfate [Prantal], methantheline [Banthine] hydrobromide, and ganglionic blocking agents [hexamethonium group]) have been developed, which enlarge this particular armamentarium.

X-ray therapy has no proved value. Recently cortisone has been successful in aborting attacks of dysidrosis, according to some observers.[8] I have been unable to confirm this observation, and hydrocortisone ointment has not proved therapeutically useful.

SUMMARY

Evidence is adduced to support the view that dysidrosis is a vesicular epidermal reaction pattern seen on the palms and soles. There appears to be no single etiologic factor. Usually the cause of dysidrosis remains unknown, but a search should be made for psychosomatic determinants, fungous infection, and mycotic or drug allergy. No support can be given the view that dysidrosis is primarily a sweat retention disorder. Principles of treatment are outlined.

8. Scully, J.: Personal communication to the author. Goldman, L.: Personal communication to the author.

SKIN HEMANGIOMA AND RETROLENTAL FIBROPLASIA

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IN THE past 10 years, coincident with the greater survival rate of premature infants, an increase in the frequency of blindness in babies has been observed. This led to the discovery of the disease entity of retrolental fibroplasia, which has a relationship to skin hemangiomas. The pathology of retrolental fibroplasia is that of hemangiomatous tissue extending from the retina into the vitreous.

It is important for the dermatologist to know about retrolental fibroplasia. In many cases there is spontaneous regression, but in the others the only possible treatment is by irradiation in the early active stage before irremedial damage, cicatrization, and blindness develop. Such treatment is still on an experimental basis. If the condition is diagnosed sufficiently early, there is some slight hope of stopping the process. Also, it is important for the dermatologist to know that impairment of vision or blindness developing after treatment of hemangiomas near the eyes may be due not to the treatment but to retrolental fibroplasia.

Reese and Blodi,[1] in a recent article on retrolental fibroplasia, state:

> The clinical onset occurs from one week to three months after birth and there is an inverse relationship between the birth weight and the age at which the first fundus changes appear. Since infants with lower birth weights manifest the disease later and infants with higher birth weights earlier, it is logical to assume that the disease might also appear in full-term infants of normal birth weight. We believe that it does, in fact, occur in full-term infants, but since the incidence in this high birth weight group is so extremely small, cases are seldom seen. We have observed the disease in its full-blown acute phase in infants eight days of age and we have on several occasions identified it in the cicatricial stage in infants born at term and of normal birth weight. In our nurseries approximately 65 per cent of premature infants weighing under 3 pounds and 30 per cent weighing between 3 and 4 pounds have the disease.

These authors estimate that as a result of retrolental fibroplasia there are probably about 700 blind babies a year in this country. The severity of the disease is unrelated to the birth weight. Although the incidence is greater among the most premature, once the process begins the course of the disease is unrelated to the degree of prematurity. The disease runs an acute or active phase lasting approximately six months. This is followed by regression and the cicatricial phase, the sequelae of which cause changes in the eye for several years thereafter. In the active

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1. Reese, A. B., and Blodi, F. C.: New York J. Med. **52**:2869 (Dec. 1) 1952.

phase there are dilatation and tortuosity of the retinal vessels and neovascularization of the periphery of the visible fundus. There may be some small hemorrhages or some clouding of the retina. Spontaneous regression may occur, or the retina may become detached at first at the periphery and later completely. In the cicatricial phase, opaque tissue is seen at the periphery of the fundus and the disk is distorted by traction toward the side of the opaque tissue, which is usually temporal. This opaque tissue eventually covers the entire pupillary area.

RELATION TO SKIN HEMANGIOMAS

Reese and Blodi point out that the clinical course of skin hemangiomas parallels that of retrolental fibroplasia in that the large majority of skin hemangiomas appear within the first few weeks after birth and undergo an active, progressive phase, which is then followed by a regressive, or cicatricial, phase. They recorded the first appearance of hemangiomas in 32 infants. Two were present at birth, and a large majority (27 of 32, or 84%) appeared within five weeks after birth. This is about the same period in which retrolental fibroplasia has its most frequent onset. The incidence of both retrolental fibroplasia and hemangiomas increases markedly as the birth weight decreases. The histologic characteristics of retrolental fibroplasia are those of angiomatous tissue budding out from the retina into the vitreous, with hemorrhage and organization. The incidence of skin hemangiomas may be higher in infants in whom retrolental fibroplasia develops. They found 20 skin hemangiomas in 80 premature infants in whom retrolental fibroplasia developed, a total of 25%. They found only 23 hemangiomas, or 11%, in 207 premature infants in whom retrolental fibroplasia did not develop. These authors state that the figures cannot be interpreted as indicating a higher incidence of skin angiomas in infants with retrolental fibroplasia, because the group of infants with retrolental fibroplasia has a lower birth weight than those without retrolental fibroplasia and it is in the lower birth weight groups that hemangiomas also have a higher incidence.

Reese and Blodi record two cases of retrolental fibroplasia associated with hemangiomas, one in which there were hemangiomas of the orbit on the side of the eye with the most advanced retrolental fibroplasia and another in which there were hemangiomas over the skin of that eye which was most affected by retrolental fibroplasia. That the incidence of retrolental fibroplasia may be higher in infants with skin hemangiomas is also suggested by these authors, although they state that their number of cases is too small to warrant general conclusions.

REPORT OF CASES

Case 1.—On June 19, 1951, the parents brought C. S., a girl 2 months of age, to see one of us on account of a hemangioma of the left lower eyelid. The baby was born prematurely at six and one-half months. The birth weight was 3 lb. 14 oz. (1,758 gm.). She was not a blue baby, but during labor the cord was prolapsed and the attending physician pushed it back in. The child cried lustily at birth. While she was in the incubator during the first week, some discoloration of the left lower lid was noticed, and this became definitely an angioma. The mother is a registered nurse. It is her first child. There is no history of birthmarks in the family. She was not sick with any of the exanthemata or in any other way during her pregnancy. The mother's father had congenital trichiasis, from which he suffered all his life and for which he had several operations.

The angioma was bulky and covered the entire left lower lid, measuring 2 by 1.5 cm. in diameter and being elevated 4 mm. above the level of the skin. Treatment of the angioma

by injections of quinine-urethan solution was begun. The baby was treated on June 19, July 16, and 25, and Aug. 2. The last week in August, when she was 4 months of age, the parents became suspicious that the child could not see, because when they took her to the light at the window the child's eyes did not seem to notice the light or their hands and other objects which they moved in front of her eyes. They then consulted their pediatrician, who referred them to an ophthalmologist, who made the diagnosis of advanced retrolental fibroplasia in each eye. The pupils were completely covered, and both retinas were entirely and irreversibly detached, because of contracture of scar tissue. He stated: "The process is entirely inactive now and has reached the end-stage. We have no treatment at all to offer . . . We noted the large hemangioma involving the left lower lid, and the left eye is the one more severely affected with retrolental fibroplasia."

Hemangioma of lid in retrolental fibroplasia (Case 1.)

Case 2.—A girl, E. J., 3 months old, was brought to one of us for treatment of a crusted, ulcerated hemangioma on the right cheek. The angioma at birth had measured 3 mm. in diameter but had grown to 2 cm. in diameter. The baby was premature and at birth weighed 2 lb. (907 gm.). On account of the ulceration and crusting, penicillin injections were started, and these were given, 150,000 units daily, for six weeks intramuscularly. The angioma was treated by radium with a satisfactory result. One month after the initial visit the child was found to be blind, owing to retrolental fibroplasia in an advanced stage with cicatrization.

The frequent coincidence of cutaneous hemangiomas and retrolental fibroplasia, particularly in premature infants, should be generally recognized among dermatologists. Premature babies of birth weights around 2 to 4 lb. (900 to 1,800 gm.) should be examined at weekly intervals during the first few months of life by an ophthalmologist. Dermatologists who encounter cases of hemangioma in premature infants should advise the parents of the importance of consulting an ophthalmologist.

DESENSITIZATION OF THE PENICILLIN-SENSITIVE PATIENT

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THIS IS a report on the desensitization of four persons who had become sensitive to penicillin and for whom penicillin therapy subsequently became necessary or imperative. The need for this desensitization and subsequent penicillin therapy became of grave importance, even mandatory, in these four persons: (1) a nurse whose sole duty was the administration of penicillin to patients in our syphilis wards; (2) a man with late syphilis of the pharynx (for whom, in our opinion, penicillin was the treatment of choice); (3) a man who had syphilitic meningitis, and (4) a man with untreated cardiovascular syphilis (aortic regurgitation).

The large-scale use of penicillin in illnesses of major and minor importance has demonstrated that this therapeutic agent, which at first was thought to be a relatively unimportant sensitizer, is able to produce reactions of grave importance (grave, chiefly, in the sense that the patient is unable to receive penicillin because of his sensitivity) as well as reactions of less importance. It is obvious that a person who has acquired a permanent or lasting sensitivity to penicillin may at some time in the future be in need of penicillin therapy because of an infection for which this antibiotic is required; this person, therefore, may have to suffer severely because his sensitivity to penicillin precludes its use, or he may have to suffer through other profound reactions if penicillin is given to him without regard to his sensitivity (Case 4).

REPORT OF CASES

CASE 1.—R. L., a white male nurse aged 60 years, gave penicillin injections to patients in the syphilis wards. Most of the penicillin used at that time was aqueous penicillin. In March, 1945, his hands began to show evidence of a dermatitis and over a period of several weeks it became so severe that he was almost unable to continue his work. Patch tests with the penicillin were positive.

Desensitization was carried out with aqueous penicillin solution, 50 units was given every three hours the first day, 100 units every three hours the second day, and 200 units every three hours the third day, the dose per injection being doubled each day until finally this patient was able to take 200,000 units per injection with no reaction. The dermatitis of the hands healed during the period of desensitization. However, during the course of this desensitizing procedure three minor exacerbations of the dermatitis occurred, and it was necessary to reduce the amount of penicillin being given in order to control the dermatitis during the period of desensitization therapy. A period of 20 days was required to produce the desired results. The dermatitis cleared during this period, and the man was able to continue his work without any evidence of further difficulty.

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CASE 2.—C. R. H., a white man aged 64 years, was seen with a gumma of the pharynx, and preparatory bismuth therapy was started, in April, 1949. This consisted of injection of 2 cc. of bismuth ethylcamphorate at weekly intervals for 12 weeks. He then received a penicillin preparation for delayed absorption, 2 cc. (600,000 units) on June 27, 28, and 29. On June 30, he presented a morbilliform eruption with many petechiae. The eruption was most marked over his chest, abdomen, back, arms, groins, and thighs and gradually faded out on the neck, forearms, and legs. A fine exfoliation occurred for 7 to 10 days, and by July 18 his skin had almost completely recovered. On Aug. 8, therapy for syphilis was resumed with bismuth ethylcamphorate and continued for eight doses. A patch test reaction to the penicillin used in the desensitizing procedure was positive. On Oct. 25, an injection of 0.1 cc. (30,000 units) of a delayed-absorption penicillin was given. Each day the dose was increased by 0.1 cc. until 1.0 cc. (300,000 units) was reached, and then it was increased by 0.2 cc. each day until 2 cc. (600,000 units) was reached; this dose was given for 15 days. During this period of penicillin desensitization and therapy no reactions were encountered.

Four months later this patient was given penicillin for pneumonia without incident.

CASE 3.—P. G., a white man with syphilitic meningitis, was known to be extremely sensitive to penicillin (on two previous occasions he had experienced a widespread erythematous exfoliative dermatitis when he was given 300,000 units of a delayed-absorption penicillin for upper respiratory infections). On Oct. 25, 1949, a desensitization regimen was undertaken. Penicillin G was dissolved in sterile distilled water so that a beginning dose of 250 units could be given. This was given every three hours. On the second day he was given 500 units every three hours, and on the third day, 1,000 units. For convenience, the penicillin was given on a three-hour schedule for five doses instead of for the eight doses. On the third day of this desensitizing regimen, an erythematous, weepy, exfoliative dermatitis of the groins and upper inner thighs developed. The dosage of penicillin was reduced, and then by carefully regulating the dose, depending upon the behavior of the dermatitis, it was possible to continue the desensitizing procedure with gradually increasing doses. By Dec. 27, 1949, doses of 10,000 units were being given, and by Jan. 19, 1950, a level of 16,000 units per dose was reached. On Jan. 28, a change was made from aqueous penicillin solutions to a delayed-absorption penicillin preparation, the beginning dose being 0.1 cc. (30,000 units). Each day it was possible to increase the dose by 0.1 cc., and on Feb. 5, 1.0 cc. (300,000 units) was reached. It was then possible to increase the dose rapidly. On Feb. 9, 600,000 units was given and this dosage was continued daily for 15 days.

Four weeks later this patient had an emergency appendectomy, and penicillin was given to him successfully.

CASE 4.—J. R., a Negro aged 64, was admitted to the hospital on Feb. 2, 1951, for pneumonitis and pleurisy. Procaine penicillin therapy (Crysticillin, 300,000 units twice a day) was started on Feb. 6; on Feb. 8, urticaria of the face made its appearance. On Feb. 10, a fine, dry, erythematous exfoliative dermatitis, chiefly of the face, was noted. The skin cleared rather promptly after discontinuation of the penicillin therapy and with the aid of soothing and palliative measures.

During his stay in the hospital the patient was found to have aortic regurgitation. His serologic tests for syphilis were positive. The spinal fluid showed no abnormal findings (he had never received treatment for syphilis). When he was dismissed from the hospital, on Feb. 25, he was referred to the syphilis clinic.

He was admitted to the syphilis clinic on March 9, and, since treatment for syphilis had been inadequate, further treatment was started. He received bismuth subsalicylate weekly until May 11. On May 18, 1951, either without consideration of or through complete oversight of the patient's previous reaction to penicillin—and, also, perhaps through the laxity and carelessness of the physician in charge—he was given 4 cc. (1,200,000 units) of penicillin procaine in oil with 2% aluminum monostearate added. Within 24 hours he was literally covered with uriticaria. His legs and arms appeared to be twice their normal size. There was also a generalized erythematous fine exfoliative dermatitis.

The skin responded well to palliative measures and in a few days appeared to be completely recovered. Thereafter he was given 2 cc. of bismuth ethylcamphorate weekly for six doses.

On July 20, chiefly through the laxity and carelessness of a physician who seemed to take lightly and did not realize the importance, severity, and intensity of the patient's two previous and recent reactions, the patient was given 1.0 cc. (300,000 units) of penicillin procaine in oil with 2% aluminum monostearate added. Within one hour, intense itching and urticaria began to appear and rapidly progressed to a generalized state. The legs and arms again were very swollen. Within a short time a generalized erythematous fine exfoliative dermatitis made its appearance. The urticaria and swelling responded promptly (within 48 hours) to treatment, and the exfoliative dermatitis was in its terminal stages in approximately 11 days.

On Sept. 19, a desensitizing regimen was started. The plan was to give designated subreactive doses of penicillin on a five-days-a-week schedule. He was given 250 units of aqueous penicillin the first day; the next day he was given 500 units, the third day 1,000 units, the fourth day 2,000 units, and the fifth day 4,000 units. The sixth dose was 8,000 units, the seventh was 10,000 units, and the eighth dose, on Sept. 27, was 15,000 units. On Oct. 1 he presented himself with a mild exfoliative dermatitis of the axillae, hands, forearms, and legs, particularly marked in the popliteal areas. The dosage of penicillin was reduced to 10,000 units. The next day he was given 12,000 units, and the same amount was given for two more days. On Oct. 5, he was given 15,000 units, and on Oct. 8, and 9, he was given 20,000 and 25,000 units respectively.

On Oct. 11, procaine penicillin in oil with 2% aluminum monostearate added was started, the patient receiving 15,000 units. The dosage was gradually increased each day and kept beneath the reaction level. On Oct. 26, the dose was 300,000 units, and on Oct. 30, a dose of 600,000 units was reached. The patient continued to receive 600,000 units at each visit through Nov. 7. On Nov. 8, he was given 1,200,000 units, and he received the same amount on Nov. 13 and 14, with no reaction whatsoever.

COMMENT

The four patients in this report were desensitized by the intramuscular administration of graded doses of penicillin, two with aqueous penicillin (Cases 1 and 3), one with delayed absorption penicillin (Case 2), and one with aqueous and delayed-absorption penicillin (Case 4). The intramuscular route seemed to be the logical one to use, since penicillin in therapeutic doses is usually administered intramuscularly. A daily schedule was used. The first patient (Case 1) was desensitized in 1945. Peck, Siegal, and Bergamini [1] reported that they had successfully desensitized a man in 1946 by using subcutaneous injections of penicillin in graded doses. Later, Peck, Siegal, Glick, Kurtin, and Bergamini [2] reported desensitizing eight persons, seven by the subcutaneous route and one by the oral route. They showed also that the penicillin used need not be just one particular type; nor is it necessary for the desensitizing schedule to be on a strict day to day basis.

In desensitizing regimens, the important factor is keeping the desensitizing doses below the reaction level of the patient's sensitivity.

Not all persons who have reactions to penicillin require desensitization. In many instances the sensitivity is relative, is transient, or is of rather minor importance, or the absolute need for penicillin in the future may not arise. A person who has urticaria from penicillin possibly may receive penicillin at some future date without subsequent reaction. This is true, also, of the minor tinea-like and/or the "id"-like reactions, and possibly, also, of any type of reaction which is of a mild or minor nature. Frequently when minor reactions occur during penicillin therapy it is not

1. Peck, S. M.; Siegal, S., and Bergamini, R.: Successful Desensitization in Penicillin Sensitivity, J. A. M. A. **134**:1546-1547 (Aug. 30) 1947.

2. Peck, S. M.; Siegal, S.; Glick, A. W.; Kurtin, A., and Bergamini, R.: Clinical Problems in Penicillin Sensitivity, J. A. M. A. **138**:631-640 (Oct. 30) 1948.

even necessary to discontinue the administration of penicillin. One must also remember that one type of penicillin preparation may cause a reaction whereas another may not.

One should concern oneself, however, with the person who has had a severe reaction, such as the serum-sickness type of reaction or the generalized erythematous type of reaction in which there is some degree of exfoliation. The latter type is frequently morbilliform in character, and at times there may be a dispersion of petechiae of greater or less degree in the involved areas. (I have seen two patients with penicillin reactions who exhibited only petechiae.) And, there have been reports[3] of severe hemorrhagic bullous reactions. Persons who have these severe types of reactions usually have a permanent or lasting sensitivity, and the further use of penicillin for these persons is precluded unless they are desensitized.

Two of the patients whose cases are herein reported (Cases 2 and 3) after desensitization were given penicillin for acute illnesses, one for pneumonia and the other for appendicitis. If these two persons had not been desensitized prior to these illnesses, they might well have suffered a more arduous convalescence. Furthermore, if patients who are sensitive to penicillin are desensitized promptly, they will not be subjected to repeated subsequent reactions, as was the case with two of our patients (Cases 3 and 4).

As a postscript to the preceding thoughts, the following observations should merit consideration. As the antibiotics gain wider and wider use, one can logically expect certain persons to become sensitized to more than one of them. To those who have acquired a lasting sensitivity to penicillin and to one or more of the other antibiotics, we owe a greater responsibility. It behooves us to desensitize them to penicillin and/or to the other antibiotic, or antibiotics, to which they are sensitive, if possible, before the urgent need for these preparations arises.

CONCLUSIONS

The occasional person who has become sensitive to penicillin and to whom it subsequently becomes necessary to give penicillin again can be desensitized; penicillin can then be given to him in full therapeutic doses.

Penicillin for delayed absorption can be used as well as aqueous penicillin solution to desensitize the penicillin-sensitive patient.

In certain specific instances the need to desensitize persons who are sensitive to penicillin should be obvious. This thought logically should be projected also to the other antibiotics.

"Drug sensitivity," notoriously difficult or impossible to overcome, seems not only possible but to be expected when the antibiotics, particularly penicillin, are involved.

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3. (*a*) Samitz, M. H.; Horvath, P. N., and Bellet, S.: Hemorrhagic Bullous Eruption Due to Penicillin G: Relationship Between Chemical Structure and Sensitizing Capacity of Penicillin G and Penicillin O, Ann. Allergy **8**:377-381 (May) 1950. (*b*) Berne, R. M.: An Unusual Sensitivity Reaction to Penicillin: Report of a Case with Autopsy Findings, New England J. Med. **242**:814 (May 25) 1950. (*c*) Lichtenstein, G. M., and Friedman, T. B.: Hemorrhagic Bullous Urticaria Treated with Corticotropin, J. A. M. A. **147**:1658 (Dec. 22) 1951. (*d*) Goldman, L.: Hemorrhagic Bullous Penicillin Reaction, in Schoch Letters, Penicillin Research Center, Southwestern Medical Foundation, Dallas, Texas, January, 1952.

ADDENDUM

Since this paper was submitted for publication, four additional patients have been desensitized. One was a nurse who had become so sensitive to penicillin by continued contact with it that continuation of her duties as a treatment nurse in the venereal disease clinic had become virtually impossible. Because of her extreme sensitivity it was necessary to begin the desensitizing procedure with an initial subreactive dose of 2 mg. of aqueous penicillin. Desensitization was not only successful but also curative of the existing severe dermatitis. These results were obtained despite the fact that there was no reduction in the degree of the patient's exposure and contact to penicillin during the desensitizing period. She is now sensitive to a brand of penicillin furnished by the State Health Department but not to any of several preparations (aqueous and delayed absorption) that has been used in this clinic for years.

FATAL SHWARTZMAN REACTION DURING ANTIBIOTIC THERAPY

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FATAL reactions during antibiotic therapy are rare, considering the number of patients who are treated with such drugs. When fatalities do occur, they should be studied and reported so that, if possible, such untoward results may be prevented, or at least treated with some success.

The case reported here was presented before the Los Angeles Dermatological Society under the title of "Fatal Penicillin Reaction Resembling Dermatitis Gangrenosa Infantum."[1] In view of the discussion at the time, and after communication with Stetson[2] and Shwartzman,[3] it is felt that a more complete presentation of the case is desirable. Furthermore, the diagnosis as presented at the Los Angeles Dermatological Society needs correction and clarification.

REPORT OF A CASE

C. C., a Mexican girl aged 5½ months, was in good health until one week previous to her first admission to Santa Barbara General Hospital for rubeola, March 31, 1951. Treatment consisted of administration of immune measles globulin, penicillin, and chloramphenicol (Chloromycetin). She made an uneventful recovery and was discharged April 6. She apparently remained well until the morning of April 12, when she became irritable. Physical examination gave essentially normal results except to reveal a rectal temperature of 102.2 F. and a dermatitis of the diaper area. The eruption was felt to be due to poor hygiene and was described as a moderate erythema with a few papules and occasional pinhead-sized vesicles. She was given an injection of penicillin procaine. The temperature increased during the day to 105 F. rectally, and the patient was hospitalized that evening. Physical examination at that time was recorded as showing an acutely ill and toxic patient. The dermatitis of the diaper area was unchanged. The anterior fontanelle was felt to be under slightly increased tension, and the neck was moderately resistant to flexion. A diagnosis of postmeasles encephalitis was considered. However, spinal fluid examination the night of admission and again on April 13 gave normal results. Supportive therapy was instituted, and additional therapy, as recorded in the table, was given. The temperature reached 105.6 F. rectally during the first two days of hospitalization but thereafter did not exceed 99 F. rectally. On April 13 the lesions over the diaper area had become hemorrhagic and some of them were covered by flaccid bullae (Fig. 1*A*). They varied in size up to 1.5 cm., and new lesions had appeared

1. Nelson, L. M., and Braslow, E.: Fatal Penicillin Reaction Resembling Dermatitis Gangrenosa Infantum, presented before the Los Angeles Dermatological Society, Los Angeles, Oct. 9, 1951.

2. Stetson, C. A., Jr.: Personal communication to the authors.

3. Shwartzman, G.: Personal communication to the authors.

on the right popliteal space and on the lower abdomen. By April 14 the lesions had increased to 2.5 cm., had become definitely gangrenous, and had coalesced to form large ulcerated areas with precipitous borders (Fig. 1*B*). There was undermining of the borders, and subcutaneous sinus tracts were present. Some lesions looked as though they had been painted with methylrosaniline. Bullae were present over the pubis, lower abdomen, and thighs. The buttocks were indurated. At this time dermatologic consultation was requested (L. M. N.), and it was suggested that the ulceration might be a manifestation of penicillin sensitization. Administra-

*Summary of Therapy**

First Admission, 3/31/51-4/6/51	Outpatient Period, 4/12/51	Second Admission 4/12/51	4/13/51	4/14/51	4/15/51	4/16/51
CCCCCCCCCCCCCCCC						
PPPPPPPP apapapap	P	apapapapapapapap				
		SSSSSSSSSSSSSSSSSSSSSSSSS				
		TTTTTTTTTTTT				
		ACTH ACTH ACTH				
		oooooooo				

* C, chloramphenicol; P, penicillin procaine; A, chlortetracycline (aureomycin); S, streptomycin; T, oxytetracycline (Terramycin); ap, aqueous penicillin; ACTH, ACTH; oooo, sulfonamide.

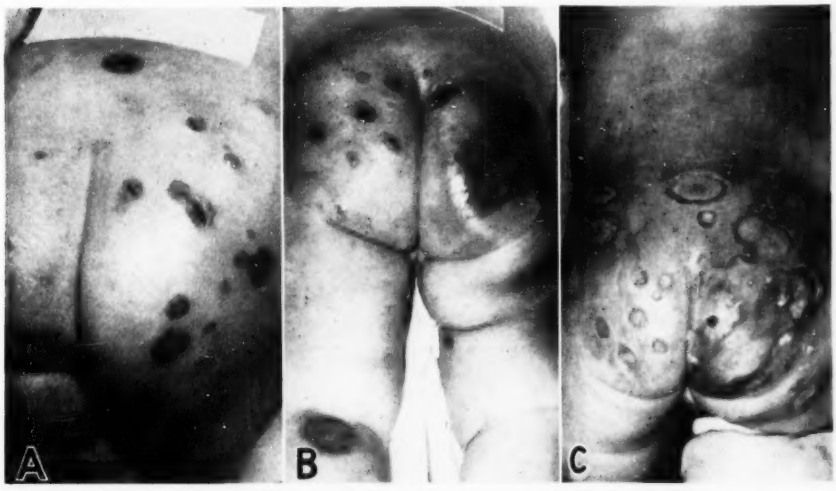


Fig. 1.—*A*, buttocks two days after onset of terminal illness, April 13. *B*, April 14. *C*, April 15, day before death of patient. (Black and white from Kodachromes.)

tion of penicillin was discontinued. However, the condition of the patient continued to deteriorate, and she died April 16, on the fifth day of her present illness.

Culture material from the ulcers grew only Proteus vulgaris, as did a blood culture taken on April 13. Smears from the bullae and from deep tissue showed many Gram-negative rods. Urinalysis was negative. A serologic test for syphilis was negative. The leucocyte count and percentage of granulocytes were as follows:

	First Admission	4/12/51	4/13/51	4/14/51	4/15/51
W. B. C.	11,400	3,500	7,750	10,300	8,600
Granulocytes	51%	42%	14%	2%	18%

Autopsy,[4] performed 13 hours after the death of the patient, showed "congestion of brain and viscera," mild meningtis, and gangrenous ulcers of the buttocks and legs. The lungs showed vascular engorgement, and the alveoli were partially collapsed. No inflammatory reaction was present. Some capillaries showed basophilic granular plugs, a few of which had nuclei resembling those of polymorphonuclear leucocytes imbedded in them (Fig. 2). Giemsa's stain[5] showed the plugs to consist of leucocytes and platelets. Microscopic examination of tissue from an ulcer showed a sparsity of lymphocytes, absence of granulocytes, and presence of numerous Gram-negative rods. A smear of the bone marrow was too poorly preserved for

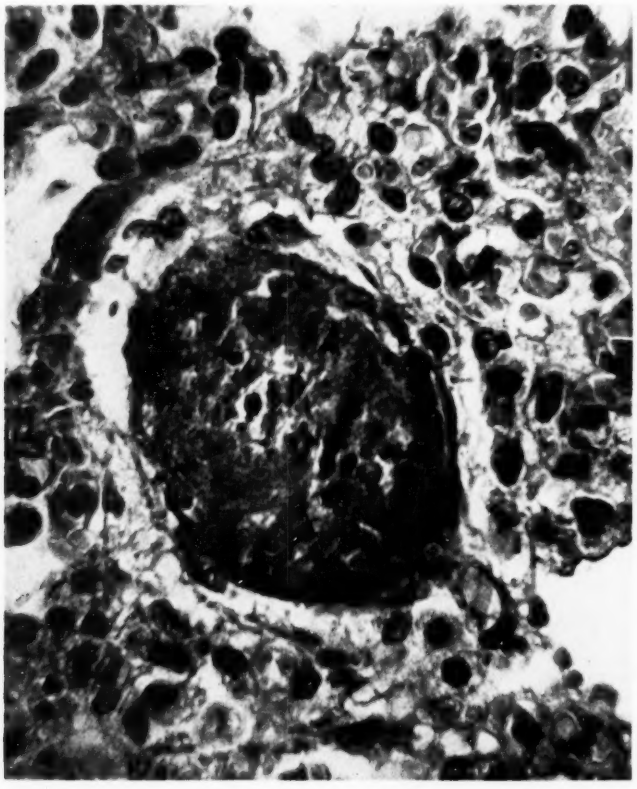


Fig. 2.—Plug in capillary of lung. (Photomicrograph by Avis Gregersen, F.B.P.A.)

detailed study, but no granulocytes with segmented nuclei were present. The fixed section showed vascular sinuses to be dilated and filled with erythrocytes. Granulocytes were in the minority and were mostly of the "stab" level or below.

COMMENT

Many of the clinical and laboratory findings of this patient have previously been noted in patients receiving penicillin, and have been attributed to that drug.

4. Performed by Dr. John P. Blanchard, pathologist, Santa Barbara County General Hospital.

5. Suggested by Dr. Nelson Paul Anderson.

Spain and Clark [6] reported on a patient whose leucocyte count fell from 13,150 per cubic millimeter at the time penicillin therapy was begun to 100 per cubic millimeter four days later. There was complete suppression of the polymorphonuclear leucocytes. The incrimination of penicillin as the cause of the leucopenia was "not conclusive," as other medication was given at the same time. No chloramphenicol was given at any time. In the case of Mears and State [7] ulceration developed around a wound while the patient was being treated with penicillin packs locally and penicillin intramuscularly; Reuben's patient,[8] who had pharyngitis and a temperature of 103 F., probably received an intra-arterial injection of the drug, followed by local sloughing. None of these cases came to autopsy, and there is, consequently, no report of capillary plugging of the lungs.

Stetson [9] has shown that in the experimental production of the Shwartzman phenomenon a profound leucopenia and neutropenia accompanied by fall of platelet count begins within a few minutes of the injection of the challenging material and that the capillaries of the lungs are sites of clumping and of retaining of most of the leucocytes and platelets.

On the basis of the clinical picture, the capillary plugs of the lungs, and the leucopenia and neutropenia, a diagnosis of fatal Shwartzman reaction was made. Platelet counts, unfortunately, were not done. It is, of course, conceivable that the leucopenia could have been due to the chloramphenicol administered during the first hospitalization.[10] Since penicillin was the only medication received previous to the development of the hemorrhagic lesions during the second hospitalization, it could possibly have been the precipitating factor. Theoretically, to incriminate penicillin one must surmise that the skin preparation resulted from contamination of the diaper area by excreted penicillin or from inadvertent intracutaneous injection of the drug on the day of the second hospital admission. The time between the previous hospitalization and the readmission (six days) is too long for the preparatory injection to remain effective. Then, one must postulate that some of the subsequent injections were given intravascularly. However, a much more likely explanation of the reaction is that advanced by Stetson [9] and Shwartzman,[3] who feel that the entire picture as presented in this patient could well be explained on the basis of local preparation of the infected sites by P. vulgaris, the bacteremia then provoking the reaction at these sites. The antibiotics would be incriminated only secondarily, in that they allowed the overgrowth of P. vulgaris.[11]

6. Spain, D. M., and Clark, T. B.: A Case of Agranulocytosis Occurring During the Course of Penicillin Therapy, Ann. Int. Med. **25**:732 (Oct.) 1946.

7. Mears, F. B., and State, D.: Arthus Phenomenon Induced by the Local Application of Penicillin, Minnesota Med. **30**:517 (May) 1947.

8. Rubens, E.: Local Hemorrhagic—Necrotic Skin Reaction Following Penicillin, J. Pediat. **38**:630 (May) 1951.

9. Stetson, C. A., Jr.: Studies on the Mechanism of the Shwartzman Phenomenon: Certain Factors Involved in Production of Local Hemorrhagic Necrosis, J. Exper. Med. **93**:489 (May) 1951.

10. Blood Dyscrasia Following the Use of Chloramphenicol, Editorial, J. A. M. A. **149**:840 (June 28) 1952.

11. Miller, C. P.: New Problems in Treatment of Infectious Diseases, Ann. Int. Med. **35**:763 (Oct.) 1951. Yow, E. M.: Development of Proteus and Pseudomonas Infections During Antibiotic Therapy, J. A. M. A. **149**:1184 (July 26) 1952.

It is quite possible that the fever noted on the first and second days of the second hospitalization was a true drug fever. The period of inoculation between the penicillin therapy given during the first hospitalization (March 31 to April 6) and that given at the time of the second hospitalization (April 12) is correct for such a development.

SUMMARY

The case of a 5½-month-old child who died four days after hemorrhagic and gangrenous ulcerations developed during antibiotic therapy is reported. It is felt that the case presents the clinical and microscopic findings of a fatal Shwartzman reaction.

30 W. Arrellaga St.

750 Mission Canyon Road.

Clinical Notes, New Instruments and Techniques

CHEILITIS DUE TO COFFEE

EMMETT S. LUPTON, M.D.
GREENSORO, N. C.

Cheilitis is frequently a difficult and baffling disorder. A patient was seen recently with cheilitis in which coffee appeared to be the offending agent. Since to my knowledge such an etiologic factor has not been reported, it seems desirable to record this case.

Cheilitis venenata is usually due to cosmetics,[1] dentifrices,[2] or medicaments.[3] Sutton and Sutton[4] reported a case of cheilitis due to the volatile oil of oranges, but doubted whether ordinary foods are often at fault. Miller[5] reported a case of cheilitis due to cinnamon in bubble gum.

A circumoral dermatitis may develop in hypersensitive children after the eating of such foods as spinach, carrots, tomato juice, and orange juice[6]; however, the vermillion borders of the lips are usually not involved.

REPORT OF A CASE

Mrs. J. S., a 39-year-old white housewife, was first seen on Oct. 29, 1951, complaining of dry, scaling, fissuring, and painful lips for the past eight months. She had been treated by several physicians and had used a variety of home remedies to no avail. Her past history revealed no evidence of allergies, nor were there any constitutional symptoms associated with the dermatitis. There was no history of medication, and on careful questioning she was unable to associate the cheilitis with any food ingestion. She had used a number of dentifrices but had not used lipstick since the onset of the cheilitis.

Examination revealed the vermillion border of the upper and the lower lip to be dry, scaly, and quite erythematous. There were a few fissures. The skin surrounding the margins of the lips was erythematous, dry, and scaling. The tongue, buccal mucosae, and gums appeared normal. There were no palpable glands in the lips.

Treatment initially consisted of warm boric acid compresses, bacitracin ointment, and 45 r of unfiltered superficial x-rays (60 kv., 5 ma., 20 cm. target-skin distance). She was then given patch tests with all her own cosmetics, soaps, and dentifrices, as well as with those used by her husband. Results of all patch tests were negative. On the treatment outlined she improved, only to relapse on Nov. 7, 1951. Careful questioning about foods elicited the history of some epigastric and substernal discomfort and eructation of gas. As coffee was the only food taken daily, she was advised to stop the use of coffee. On Nov. 16, 1951, her lips were almost entirely well, and her indigestion had disappeared. A patch test of the liquid coffee with use of the

1. Zakon, S. J.; Goldberg, A. L., and Kahn, J. B.: Lipstick Cheilitis: Common Dermatosis; Report of 32 Cases, Arch. Dermat. & Syph. **56**:499-505 (Oct.) 1947. Sulzberger, M. B., and Hecht, R.: Acquired Specific Hypersensitivity to Simple Chemicals: Further Studies on the Purification of Dyes in Relation to Allergic Reactions, J. Allergy **12**:129-137 (Jan.) 1941. Schonberg, I. L.: Dermatitis Due to Liquid Lip Rouge, Arch. Dermat. & Syph. **45**:152-153 (Jan.) 1942.

2. Beinhauer, L. G.: Cheilitis and Dermatitis from Tooth Paste, Arch. Dermat. & Syph. **41**:892-894 (May) 1940. Templeton, H. J., and Lunsford, C. J.: Cheilitis and Stomatitis from ST37 Tooth-Paste, ibid. **25**:439-443 (March) 1932.

3. Goldman, L.: Cheilitis from Local Use of Penicillin Solutions in the Mouth: Report of a Case, Arch. Dermat. & Syph. **53**:133-134 (Feb.) 1946.

4. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, Ed. 10, St. Louis, C. V. Mosby Company, 1938, p. 1484.

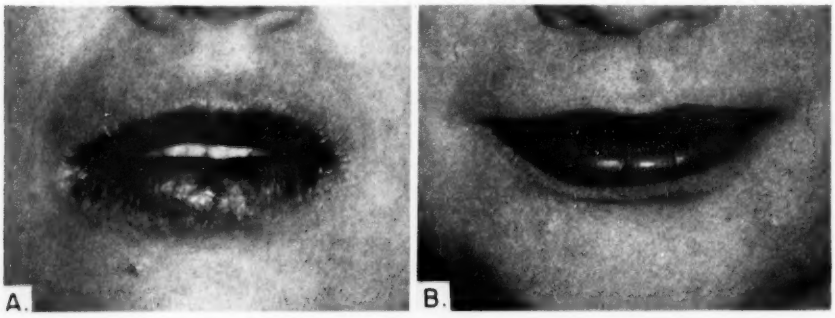
5. Miller, J.: Cheilitis from Sensitivity to Oil of Cinnamon Present in Bubble Gum, J. A. M. A. **116**:131-132 (Jan.) 11) 1941.

6. Urbach, E., and Gottlieb, P. M.: Allergy, Ed. 2, New York, Grune & Stratton, Inc., 1943, p. 707.

same concentration that she drank gave a 2+ reaction. The patch was applied to the flexor surface of her left forearm for 48 hours.

She remained well during the next three months. On request she drank one cup of coffee on Feb. 2, 1952. In 12 hours her lips became tender, erythematous, and dry. Scaling and considerable discomfort followed. Her lips promptly cleared with stopping of coffee ingestion, and with application of boric acid compresses and bacitracin ointment.

Beginning on May 15, 1952, she drank a total of five cups of coffee over a three-day period, and her lips became swollen, red, tender, and scaling once more. Local treatment was again instituted; coffee ingestion was stopped, and she has been clear to this date.



Cheilitis due to coffee. *A*, on Feb. 4, 1952. *B*, on Feb. 18, 1952, after use of coffee was discontinued and treatment was given.

Questioning revealed that she did not drink the coffee excessively hot and that no other member of her family was similarly affected. She was able to drink hot tea during the same time with no untoward effect.

The evidence seems adequate to incriminate coffee in this instance. A patch test of coffee gave a positive reaction. Twice afterward the patient had a relapse after drinking coffee. The eruption subsided when the use of coffee was discontinued.

NIKOLSKY SIGN

Page from "Notable Contributors to the Knowledge of Dermatology"

HERMAN GOODMAN, M.D.
NEW YORK

Nikolsky, Pyotr Vasilyewich, or Pierre W. Nikolsky, was born in Usman, Tambow, Russia, in 1858 (some biographic references give 1855). He studied at Kiev. He became an assistant of Stoukowenkow at Kiev (1884 to 1935) and served in the skin clinic. Nikolsky became professor, first at Warsaw, in 1900, then at Rostov, as was announced at the Budapest Kongress. Nikolsky presented "L'etat de la dermatologie et de la syphiligraphie en Russie jusqu'à 1884." He wrote that he saw the Russian dermatology from its infancy.

Nikolsky is best known for his contribution of 1896, which earned him the eponym, Nikolsky's sign. A German translation of the Russian title was "Material zur Lehre von Pemphigus Foliaceus, Cazenave, Kiev." Nikolsky made this reference to the subject: "Ce fut le Prof. Stoukowenkow qui le premier diagnostiqua un cas de pemphigus foliaceus Cazenave et ce fut sur 5 cas de cette maladie que je basai ma dissertation, dans laquelle j'étudiai le symptôme de cette affection—instabilité de la couche cornée (diminution de l'adherence entre les couches épidermiques)—qui plus tard fut universellement connu sous le nom de signe de Nikolsky. . . ." (Budapest Kongress).

Nikolsky wrote a number of papers and books. A few appeared in French. The greater number were in Russian. The following were some of the titles: "L'élimination du mercure par le sang menstruel au cours du traitement mercuriel" (*La Syph.* 1904, Y. 1, No. 7); "Deux cas de gangrène de la fesse consécutive à une injection mercurielle" (*Bull. Soc. franç. dermat. et syph.*, 1906); "Statistique de la syphilis et du chancre mou parmi les prostituées inscrites de Kiew" (*Revue de morale progressive*, 1889); "Le dermographisme rouge et blanc" (*Bull. Soc. franç. dermat. et syph.*, 1902); "L'importance des reflexes vaso-moteurs de la peau alterée dans la therapeutique des maladies dermiques" (*Bull. Soc. franç. dermat. et syph.*, 1924); "Le dermatographisme blanc sur la peau rouge" (*J. mal. cutanées et syphilitiques*, 1908). English translations of other titles were as follows: "Lectures on Treatment of Syphilis" (1905); "General Therapy of Skin Diseases" (1910); "Introduction to Treatment of Syphilis and Skin Diseases" (1925); "Syphilis and Venereal Diseases" (second edition, 1928); "Skin Diseases" (third edition, 1928).

Dr. Eugene Cahan, hematologist at Sydenham Hospital, (through the courtesy of Dr. Theodore Rosenthal) has made the following translation from the Russian of Prof. P. V. Nikolsky's "Diseases of the Skin," second edition, State Publishers, 1927, page 135 (pemphigus Foliaceus Cazenave):

". . . and according to my observations the skin shows a weakening relationship and contact among its layers (namely between corneal [horny] and granular layers) on all surfaces even in places between lesions [blisters and excoriations] on the seemingly unaffected skin. This characteristic behavior of the skin may be disclosed by two methods—(1) by pulling the ruptured wall of the blister, it is possible to take off the horny layer for a long distance, even on a seemingly healthy skin; (2) the rubbing off of the epidermis between the bullae by slight friction without breaking the surface of the skin and leaving moist surface of the granular layer."

Available biographical sources failed to disclose any date of death. The New York offices of the government of the U. S. S. R. were not helpful. It is assumed that Dr. Nikolsky is dead.

TRICHOPHYTON SULFUREUM IN SOUTHERN OHIO AREA

CLAUDIA R. SIMON, M.D.
AND
JAN SCHWARZ, M.D.
CINCINNATI

In the recent literature an increased number of tinea capitis infections due to Trichophyton sulfureum in the southwestern United States have been reported by Howell, Wilson, and Caro. These cases occurred mainly in Texas and California and were thought to be secondary to similar outbreaks in Mexico.[1] Cases have also been reported by Franks and associates[2] and by Georg[3] among Puerto Ricans who had recently immigrated to New York City.

An extension of this fungus toward the more central parts of the United States was predicted. Recently three cases in one family were reported from Pennsylvania.[4] Occasional

From the Department of Dermatology and Syphilology of the College of Medicine of the University of Cincinnati and the Laboratory of Mycology of the Cincinnati General Hospital.

1. Howell, J. B.; Wilson, J. W., and Caro, M. R.: Tinea Capitis Caused by Trichophyton Tonsurans (Sulfureum or Crateriforme), A. M. A. Arch. Dermat. & Syph. **65**:194-205 (Feb.) 1952.

2. Franks, A. G.; Rosenbaum, E. M., and Mandel, E. H.: Trichophyton Sulfureum Causing Erythema Nodosum and Multiple Kerion Formation, A. M. A. Arch. Dermat. & Syph. **65**:95-97 (Jan.) 1952.

3. Georg, L. K.: Trichophyton Tonsurans Ringworm: New Public Health Problem, Pub. Health Rep. **67**:53-56 (Jan.) 1952.

4. Scully, J. P.: Trichophyton Sulfureum Infection in One Adult and Two Children of a Family, A. M. A. Arch. Dermat. & Syph. **65**:633-634 (May) 1952.

scattered cases have been reported in a number of states. The mycology laboratory of the Communicable Disease Center in Atlanta has recently received a positive culture from Indiana.[3]

The following are case reports of T. sulfureum infections in southern Ohio.

REPORT OF CASES

An 11-year-old white boy was first seen in the outpatient dispensary of the department of dermatology on Feb. 14, 1952. He had several irregular areas of alopecia of the scalp. Short broken-off hairs were present in these areas. There was no fluorescence under Wood's light. A culture of a broken-off hair revealed yellow colonies of T. sulfureum on Sabouraud's dextrose agar. The patient was seen again on April 17 and had had no treatment in the interim. The patches of alopecia had increased in size and now showed a blue-gray fluorescence under Wood's light. A second culture taken at this visit was again positive for T. sulfureum. Epilation by x-ray was then done.

The child has always lived in Ohio, except for two trips to Kentucky in 1951. There are no animal pets in the family. The patient's brother had tinea capitis due to Microsporon audouini in October, 1951.

Two additional patients with T. sulfureum infections of the glabrous skin were observed. In both the lesions had the typical annular papulosquamous appearance of tinea corporis. One of these patients, a 10-year-old white girl, was first seen on March 6, 1952, and had such a single lesion on her right shoulder. When seen again, on April 24, 1952, the lesion had disappeared under topical therapy with Furaspor (1% nitrofurfuryl methyl ether in a vanishing cream base).

The other patient, a 9-year-old Negro girl, was first seen on April 10, 1952, and had a single annular lesion of her right knee. She is improving under topical therapy with Furaspor.

Attempts to establish the sources of infection in these cases have so far been unsuccessful. No contacts with T. sulfureum have been uncovered; however, the search is being continued.

The preceding report indicates that T. sulfureum is spreading also in the more central parts of the United States. We suspect, as others have, that this organism, causing infections difficult to detect and difficult to treat, may be responsible for our future tinea capitis problems.

ANGULAR STOMATITIS TREATED WITH SILICOTE OINTMENT

A. J. REICHES M.D.
ST. LOUIS

Ariboflavinosis is the cause of many cases of angular stomatitis, but accumulating experiences have shown that not all cases are due to a specific riboflavin deficiency. Moore, Minnich, Vilter, and Spies,[1] and Ellenberg and Pollack [2] have used the name pseudoariboflavinosis for such cases. In this term is included (1) angular stomatitis which may be caused by the trauma of placing poor-fitting artificial dentures or by dental malocclusions and (2) angular stomatitis caused by sensitizing and irritating substances, like tooth powders and pastes, mouth washes, and, more recently, the antibiotics, such as penicillin, chlortetracycline (aureomycin), oxytetracyclin (Terramycin), and chloramphenicol. I prefer the term angular stomatitis to designate maceration and cracking of the mouth. The term "perlèche" should be discarded, because historically it implies an impetiginous origin.[3] The name "cheilitis" is also confusing and has too broad a connotation.

1. Moore, C. V.; Minnich, V.; Vilter, R. W., and Spies, T. D.: Hypochromic Anemia in Patients with Deficiency of Vitamin B Complex: Response to Iron Therapy with and without Yeast, J. A. M. A. **121**:245-250 (Jan. 23) 1943.

2. Ellenberg, M., and Pollack, H.: Pseudo Ariboflavinosis, J. A. M. A. **119**:790-792 (July 4) 1942.

3. Stannus, H. S.: Some Problems in Riboflavin and Allied Deficiencies (Lumleian Lectures, Abridged), Brit. M. J. **2**:140 (July 29) 1944.

The treatment of pseudoariboflavinotic angular stomatitis depends on the finding and discontinuance of primary irritants and sensitizing substances. If antibiotics are being used, the transitory angular stomatitis usually clears soon after use of the antibiotic is stopped. However, conditions occurring as a result of dental malocclusions, poor-fitting dentures, or of other chronic traumatic origin are often difficult to treat. Corrections of malocclusions and of artificial dentures and the protection of the irritated area from saliva are not easily obtained.

Results for 13 patients who had angular stomatitis not caused by ariboflavinosis are herein reported. For these patients I have found the use of Silicote ointment (an ointment compounded of 30% silicone oils in a petrolatum base) containing 3% boric acid or 2% ammoniated mercury very practical. Five of the patients had ill-fitting dentures. Consistent results were obtained on the other eight, whose conditions were healed after three to eight days of this local treatment. Among the five patients with the ill-fitting dentures as an obvious cause, four had comparatively good results, but one had a recurrence one week after discontinuance of treatment but promptly responded again to Silicote ointment.

Talbot, MacGregor, and Crowe [4] have reported the use of water-resistant Silicote ointment, and I feel that it is a distinct aid in the treatment of these conditions.

SUMMARY

Water-resistant Silicote ointment (30% silicone oils in a petrolatum base) with the addition of ammoniated mercury or boric acid is a useful supplement in the treatment of angular stomatitis.

4. Talbot, J. R.; MacGregor, J. K., and Crowe, F. W.: The Use of Silicote as a Skin Protectant, J. Invest. Dermat. **17:** 125-126 (Sept.) 1951.

TREATMENT OF PUSTULAR PSORIASIS AND PUSTULAR BACTERID WITH QUINACRINE (ATABRINE)

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NEW YORK
AND
MAURICE H. NOUN, M.D.
DES MOINES, IOWA

Recently a patient with discoid lupus erythematosus and an incidental severe psoriasis complicated by pustular psoriasis of the palms and soles was treated with quinacrine hydrochloride (Atabrine Dihydrochloride). When he was reexamined after a three-week interval some improvement in the lupus erythematosus was noted. Surprisingly, all the lesions of pustular psoriasis had disappeared, while those of the extensive psoriasis over the body had involuted some 95%. This observation has prompted the use of the drug in two additional cases of psoriasis with pustular lesions of the palms and soles and in two cases of pustular bacterid. A brief report of these cases is thought to be of general interest.

REPORT OF CASES

CASE 1.—F. B., a 52-year-old white man, had an extensive psoriasis which developed in 1947. Chronic disseminated discoid lupus erythematosus, with recurrent bouts of mild fever suggesting possible transformation to the subacute type, was noted in 1949. The lupus erythematosus was controlled with conventional measures, including avoidance of the sun. An intensive local and dietary regimen was prescribed for the psoriasis, but improvement was not obtained. In November, 1949, after chloramphenicol (Chloromycetin) therapy for a concomitant prostatitis, the lesions of psoriasis became much worse, and severe pustular psoriasis developed over the palms and soles. Another exacerbation occurred after he had had aureomycin therapy for pneumonia in June, 1952. On examination in November, 1952, residual lupus erythematosus was present; the psoriasis was severe, with large thick "geographic" plaques on the trunk and extremities, and severe pustular psoriasis on the palms and soles.

Quinacrine hydrochloride, 100 mg. three times a day, was prescribed for the lupus erythematosus. Ten days later all the lesions of pustular psoriasis had disappeared, and the scattered psoriatic lesions were greatly improved. After another three weeks of therapy, improvement was maintained, and the extensive psoriasis had nearly disappeared. Lesions of lupus erythematosus were mildly improved. The pustular psoriasis recurred mildly five days after temporary discontinuance of quinacrine therapy, but again cleared rapidly on resumption of the drug, in a dose of 200 mg. per day.

CASE 2.—F. J., a 36-year-old white woman, had patches of pustular psoriasis on the palms and soles of five months' duration. Thickened psoriatic patches were present on the elbows. There was no response to five superficial x-ray treatments and to fungicidal preparations. The eruption was accompanied by intense itching, especially at night. Quinacrine therapy was initiated in a dose of 100 mg. daily and increased to 300 mg. daily. After one week most of the pustular lesions had involuted, and itching was no longer a problem. Complete involution of the pustular lesions was noted after the third week.

CASE 3.—L. H., aged 54, a white woman, presented erythematous and infiltrated patches of pustular psoriasis on the palms and fingers. She also had well-defined patches of psoriasis in the scalp. Treatment with compresses, aureomycin ointment, and oxytetracycline (Terramycin) orally for one week was of little value. Quinacrine therapy was then instituted in a dose of 100 mg. increasing to 300 mg. daily, and after three weeks the pustular lesions had disappeared.

CASE 4.—E. N., a 50-year-old white man, had an acute dermatophytosis which developed in September, 1951. A vesicular dermatophytid supervened, but on the involution of the fungous infection continued in vesiculopustular form on both palms. This eruption persisted to date of the first examination (February, 1953), despite a full course of x-rays and various types of local and systemic therapy during some 30 visits to a dermatologist. The patient was some 30 lb. (14 kg.) overweight. Of 10 remaining teeth, 8 were grossly infected; gingival recession and infection were present as well. X-rays disclosed apical infection. On examination, multiple erythematous patches were present on the palms, especially on the thenar and hypothenar eminences. Superimposed on this were multiple deep-seated vesicular pustules. There was considerable accompanying tenderness. A diagnosis of pustular bacterid was made and therapy was instituted with quinacrine hydrochloride, 100 mg. daily, increasing in three days to 300 mg. Within 10 minutes after the first administration of quinacrine, four new pustular lesions appeared. Improvement began in two days, and on the second examination two weeks later the eruption had disappeared. The patient was given a 1,400 Cal. diet, and arrangements were made for the removal of the diseased teeth. Therapy is being maintained with 100 mg. of quinacrine hydrochloride daily.

CASE 5.—L. R., a 26-year-old housewife, presented circumscribed erythematosquamous patches with numerous pustular lesions, involving the palms and soles. The process was of two months' duration. This patient had been treated previously by another physician for a fungous infection with several fungicidal preparations. A microscopic examination of scales failed to reveal mycelial threads. The lesions were resistant to routine treatment for psoriasis. The patient was willing to try quinacrine therapy, as other measures had been ineffectual. The dosage of quinacrine hydrochloride was 100 mg. three times a day for one week, 100 mg. twice a day for the second week, and 100 mg. daily the third week. After the third week, all the pustules had disappeared, leaving only a residual redness. The patient has been free of pustular lesions for two additional months.

SUMMARY

Three patients with pustular psoriasis occurring in conjunction with psoriasis elsewhere on the body were treated with quinacrine hydrochloride (Atabrine Dihydrochloride). All the pustular lesions involuted within a three-week interval.

One of the patients with pustular psoriasis had extensive, inveterate, treatment-resistant psoriasis, with the lesions scattered over the body; these scattered lesions involuted 95% after three weeks of quinacrine therapy.

Two patients with pustular bacterid were treated with a quinacrine; all the pustular lesions disappeared within a three-week interval.

The lesions of pustular psoriasis reappeared promptly in one patient after temporary interruption of therapy; the pustular lesions again disappeared after reinstitution of quinacrine therapy.

Society Transactions

CLEVELAND DERMATOLOGICAL SOCIETY

Irving L. Schonberg, M.D., *President*

John R. Haserick, M.D., *Secretary*

George M. Stroud, M.D., *Reporter*

Jan. 22, 1953

Chronic Discoid Lupus Erythematosus. Presented by Dr. E. L. Glicksberg.

In May, 1952, M. F., a white woman aged 33, first noticed the appearance of a circular, raised lesion in the left maxillary area. It was purplish and swollen and had a red border. In December, 1952, her left ear lobe became swollen, red, and distended. This lasted for about a week and is now subsiding.

The patient had a "nervous breakdown" in 1944. She had one miscarriage at the 10th week of pregnancy in 1949. From April to November, 1949, the patient had a moderately severe seborrheic dermatitis of the scalp and groin.

The general physical condition is normal. Cutaneous examination reveals a circular, superficial, papular inflammatory lesion in the left maxillary area. It has an erythematous, indurated border and is clearing in the center, with atrophy. No crusts are present. The left ear lobe is slightly edematous.

The hemogram and urine were normal. A roentgenogram of the chest was normal. Serologic tests of the blood were negative.

Histologic examination of a biopsy specimen was reported as follows: "A moderate amount of hyperkeratosis is seen throughout the section. In areas this process is found in dilated follicular orifices. The remainder of the epidermis is slightly atrophic, with the rete pegs effaced for the most part. There is mild hyperpigmentation of the basal-cell layer. The papillary layer of the corium is the seat of moderate parenchymatous edema. A sparse focal infiltrate is seen in this area, limited to the perivascular regions. This is composed almost entirely of lymphocytes.

"The blood vessels show considerable dilatation of the lamina, with no change, however, in the vessel walls.

"In the midcorium a similar focal infiltrate is found surrounding the vessels, as well as the adnexa. The entire midcorium is the seat of edema, both interstitial and parenchymatous, with the blood-vessel lumina markedly dilated. The findings are compatible with those of early chronic discoid lupus erythematosus."

Treatment has consisted of four injections of bismuth subsalicylate, and the lesion is gradually subsiding.

DISCUSSION

Dr. J. R. Haserick: This disease is rather difficult to classify. The microscopic picture is so predominantly lymphocytic that we have been prone to call it a lymphocytic lupus erythematosus, the differential diagnosis being between that and lymphocytoma. Interestingly enough, the patient responded very well to bismuth. In our group of 10 patients none has shown any internal manifestations of disease—increased sedimentation rate, a positive L. E. test, or anything of that type. They are photosensitive.

Case for Diagnosis: Erythroplasia of Queyrat? Presented by Dr. Melvin Brody.

Herpes Zoster. Presented by Dr. Benjamin Levine.

Alopecia Areata. Presented by Dr. Benjamin Levine.

Subcutaneous Fat Necrosis of the Newborn. Presented by Dr. E. L. Glicksberg.

Numerous Multiple Pigmented Nevi with Subcutaneous Nodules (Neurofibromata?). Presented by Dr. I. L. Schonberg.

Pemphigus Vulgaris. Presented by Drs. Melvin Brody and E. L. Glicksberg.

Acanthosis Nigricans or Nevus Unius Lateris. Presented by Dr. John E. Rauschkolb.

Case for Diagnosis: Keratosis Follicularis? Presented by Dr. Benjamin Levine.

Xanthoma Tuberosum Multiplex. Presented by Dr. N. R. Krupkin (by invitation).

Epidermoid Carcinoma of the Nose with Metastasis to the Submaxillary Area and Thoracic Glands. Presented by Dr. I. L. Schonberg.

A Case for Diagnosis: 1. Duhring's Disease? 2. Epidermolysis Bullosa? Presented by Dr. Gerard A. DeOreo.

Irving L. Schonberg, M.D., *President*
John R. Haserick, M.D., *Secretary*
George M. Stroud, M.D., *Reporter*
Feb. 26, 1953

Chronic Discoid Lupus Erythematosus. Presented by Drs. George H. Curtis and E. S. Kozikowski.

Mr. P. F. K., aged 41, a white commercial fisherman on Lake Erie, has had a facial eruption since August, 1952. He has been exposed to sunlight and the elements to a considerable extent; he goes hatless and becomes deeply tanned in summer but never has an acute "sunburn." Oftentime the exposed surfaces are covered with tar dust from fishing nets.

There were about 10 lesions on the front and sides of the face, one of which showed atrophic scarring and follicular plugging.

The routine hemogram determination, urinalysis, and blood sugar estimate gave values within normal limits. The blood serologic tests and the L. E. test (plasma-dog marrow) gave negative results. A roentgenogram of the chest showed a normal condition.

A biopsy from the left temporal region was reported as follows: "There is a thin, laminated, hyperkeratotic scale with a few focal areas of parakeratosis. The epidermis shows slight atrophy, with flattening of the rete pegs. There is liquefaction degeneration of the basal layer. There is homogenization beneath the epidermis, and below this a rather heavy, nonspecific inflammatory reaction. Lymphocytes are seen diffusely throughout the upper cutis and are also well localized in the perivascular areas. The diagnosis is chronic discoid lupus erythematosus."

From Dec. 1, 1952, to Jan. 8, 1953, quinacrine (Atabrine) hydrochloride was administered in doses of 0.1 gm. twice daily, and subsequently once a day. There has been about 95% improvement, and many of the lesions have disappeared. The three oldest lesions persist but have receded considerably.

Systemic Lupus Erythematosus: Failure of Quinacrine to Maintain Cortisone- and Corticotropin-Induced Remission. Presented by Drs. J. R. Haserick and K. H. Burdick.

Mrs. S. S., white, aged 28, in June, 1951, after the delivery of a premature child (6½ months gestation age), noted the onset of weakness, followed in a few days by a temperature of 100 to 102 F. and stiffness and swelling of the joints. A butterfly erythema developed over the face, in association with severe ulceration of the buccal mucosa and gums. The past history revealed many illnesses, including typhoid in Germany in 1948 and meningitis, diagnosed at Cleveland City Hospital, in 1949. Her history by systems revealed many minor complaints. Raynaud's phenomenon was noted beginning in 1947.

Examination on admission revealed the temperature to be 101 F., the pulse rate 100, and the blood pressure 96/50. Positive physical findings included a violaceous erythema over the bridge of the nose and cheeks, with an erythematous, exudative aphthous type of ulceration over the hard palate and buccal mucosa. Cyanosis of the toes and fingers was noted. The fingers blanched white after a short exposure to cold.

On admission on Sept. 25, 1951, the hemoglobin was 9 gm. per 100 cc., and the leucocyte count 3,200, with 48% neutrophiles, 32% lymphocytes, 6% monocytes, and 14% atypical cells. The plasma-dog marrow L. E. test was positive. The sedimentation rate was increased to 1.55 mm. in one minute (normal, 0.45 mm.). Routine urinalysis gave normal findings. Plasma protein determination by the Tiselius method revealed a striking increase in gamma globulin of 37% over normal (normal range, 8.6 to 14.8 gm. per 100 cc.).

The patient responded promptly to cortisone and corticotropin. Treatment with quinacrine hydrochloride, in a dose of 0.1 gm. twice a day, was begun on Nov. 21, 1952. At this time she was taking 25 mg. of cortisone and 10 mg. of corticotropin daily. On Feb. 9, 1953, the doses of cortisone and corticotropin were diminished, while the quinacrine dosage was maintained. On the fourth day after steroid therapy was discontinued, the patient noted the onset of fever, malar flush, and recurrence of lesions on the mucous membrane. Steroid therapy was resumed, with prompt disappearance of the fever and other symptoms, including her joint stiffness. The L. E. test was negative prior to discontinuation of the steroid therapy but positive after the flare-up.

DISCUSSION

DR. G. H. CURTIS: The first case was presented to show the effect of quinacrine both on the lesions of lupus erythematosus and on the pigmentation of the skin. All but 3 of the 10 lesions over his face have disappeared, and I think that there were one or two on the scalp. They began to disappear within about a week after the beginning of the administration of quinacrine. He has been on quinacrine therapy now for several months. One of the things that bothers me is how long the administration of quinacrine can be continued. I presume we shall have to withdraw the quinacrine for a while and see what happens. I do not know anything about the pharmacology of quinacrine except that indirectly I heard that it shielded from ultraviolet radiation. If anyone has any other information, I should like to know about it.

DR. G. M. STROUD: In the original article on the treatment of lupus erythematosus with quinacrine, the author thought there must be some effect beyond the shielding from sunlight because in one case some of the joint symptoms subsided.

DR. H. N. COLE: My colleagues and I have been using quinacrine since last February, and it is my impression that results from the drug, if any, will begin to show within a month or so. Once in a while you will see a patient who does not respond. We have had something over 30 patients so treated, and two or three of them have been resistant to it and have had a dermatitis, so that we had to discontinue use of the drug.

DR. H. H. JOHNSON: In the Army it was estimated that the incidence of lichenoid dermatitis was from 1 in 1,000 to 1 in 2,000 persons. Our rough estimate at Moore General Hospital was from 1 in 500 to 1 in 1,000. With lichenoid dermatitis I do not believe that the weather was an important factor, but that it was a question of how much quinacrine was given and for how long. A number of cases were found in the Italian Theater, but the incidence was much lower, since quinacrine was not taken over a long enough period, usually only for two or three months in the malarial season. The maximum incidence occurs five to eight months after quinacrine was started. Only 20% exhibited the dermatitis in the first three months, on a dose of 0.1 gm. or more daily. Some also had an exfoliative dermatitis. The incidence of the latter was relatively low, and the patients were usually evacuated from the area because of the severity of the eruption. A very small dose will cause a remarkable flare-up of the exfoliative dermatitis, in contrast to the long-term administration necessary for recurrence of lichenoid dermatitis.

Rosacea Acuminata (Crocker). Presented by DRS. G. H. CURTIS and K. H. BURDICK.

Pityriasis Lichenoides Chronica (Parapsoriasis en Goutte). Presented by DR. G. H. CURTIS and R. ROBISHAW.

Syringocystadenoma. Presented by DRS. J. R. HASERICK and G. D. CHIRELLI.

Secondary (Postinfectional) Macular Atrophy (Atrophoderma Maculosum Syphiliticum). Presented by DRS. JOHN E. RAUSCHKOLB and GILBERT H. BARNES.

Multiple Benign Tumor-like Growths of the Skin (Schweninger and Buzzi Disease). Presented by DRS. E. W. NETHERTON and F. J. ROGERS.

Scleroderma and Systemic Lupus Erythematosus in Remission on Cortisone and Isoniazid. Presented by DRS. JOHN R. HASERICK and A. A. SCHERBEL.

Systemic Lupus Erythematosus—Remission for Two Years After Nitrogen Mustard and Cortisone. Presented by DRS. JOHN R. HASERICK and K. H. BURDICK.

Acnitis. Presented by DRS. GEORGE H. CURTIS and E. S. KOZIKOWSKI.

Mycosis Fungoides. Presented by DRS. E. W. NETHERTON and G. D. CHIRELLI.

Mycosis Fungoides. Presented by DRS. JOHN R. HASERICK and F. J. ROGERS.

Erythema Induratum. Presented by DRS. GEORGE H. CURTIS and F. J. ROGERS.

Sporotrichosis, Localized Lymphatic Type. Presented by DRS. JOHN E. RAUSCHKOLB and GILBERT H. BARNES.

Dermatitis Herpetiformis. Presented by DRS. E. W. NETHERTON and R. ROBISHAW.

Case for Diagnosis: Dermatitis Herpetiformis? Presented by DRS. G. H. CURTIS and R. ROBISHAW.

MANHATTAN DERMATOLOGIC SOCIETY

Jack Wolf, M.D., President

George M. Lewis, Secretary

Jan. 13, 1953

Congenital Cicatrizing Annular Band of the Forearm. Presented by DR. ORLANDO CANIZARES.

C. D., an infant girl aged 7 months, shortly after birth was noticed by her parents to have constricting bands about the forearms. Otherwise the infant was normal. There is no history of a similar deformity in the family.

Examination is essentially normal except for a deep cicatrizing annular band at the level of the distal third of the left forearm. The soft tissues of the left hand, especially on its dorsal aspect, seem slightly edematous. There are no changes in the color of the skin. The cicatrizing band in its dorsal aspect is about 1 cm. higher than in its flexor aspect. For this reason it does not form a complete ring. On the right forearm there is a similar, but less pronounced, groove at the same level, noticeable only on the flexor aspect.

Roentgenograms showed soft-tissue constriction at the distal third of the left forearm. No bony changes were noted.

DISCUSSION

DR. DAVID BLOOM: There are a number of reports of annular constricting bands on fingers and toes with or without congenital amputation of a digit or of a hand or foot. The prevailing opinion is that these developmental abnormalities are not produced by constriction of an amniotic band. They are congenital malformations of hereditary nature. I do not think the cosmetic aspect warrants an operation.

DR. PERRY SACHS: One wouldn't expect to find symmetry if the band were due to fetal position. A biopsy should be considered, and if fibrosis is found, a surgical procedure, such as plastic repair, would be indicated. This may obviate future changes due to mechanical embarassment of the circulation.

DR. NATHAN SOBEL: I believe a plastic procedure should be carried out on one of the constrictions anyway. Various methods have been tried, and I should like to see a plastic operation attempted.

DR. WILBERT SACHS: One should get a history of the type of delivery; for example, Bandl's ring may possibly form a constriction at the point where the part is constricted.

DR. DAVID BLOOM: If this constriction were due to a fibrous ring, as in ainhum (dactylolysis spontanea) an operation would be justified, but I do not think it is.

DR. ORLANDO CANIZARES: Wells and Robinson (Wells, T. L., and Robinson, R. C. V.: Annular Constrictions of the Digits, A. M. A. ARCH. DERMAT & SYPH. **66**:569 1952) mention similar conditions. They cite Johnson (Johnson, H. M.: Congenital Cicatrizing Bands: Report of Case with Etiologic Observations *Am. J. Surg.* **52**:498, 1941), who reported the same type of band in the lower third of the leg. Nothing was done, and the foot became enormous because of the vascular changes that occurred. There has been much discussion as to the etiology of this condition, and it was even thought that the umbilical cord could have been wrapped around the affected extremity. This patient has rather symmetrical lesions, although one is not very marked. Focal necrosis of the limb bud tissue occurring in the developmental embryonic stage seems the most plausible explanation of this condition. As to therapy, I hesitate to let it go without treatment for too long a time, because it seems to me that one hand is already a little swollen. Something should be done soon, and perhaps this might best be plastic surgery, with grafting if necessary.

DR. ANTHONY C. CIPOLLARO. I suggest leaving it alone and watching it, since we do not know what, specifically, to operate on.

Case for Diagnosis: Pemphigus? Presented by DR. SAMUEL PECK.

M. L., a woman aged 37, has had lesions of the buccal mucosa, hard and soft palates, tongue, and uvula, for 3 years; an eruption on the chin for 1 year, and corneal ulcerations and repair, for 10 years. In 1942 the patient had a convergent strabismus with corneal ulcers of the right eye. In 1943 the Mantoux test gave a positive reaction to tuberculin in a dilution of 1:100,000. Biopsy of the keratitic tissue proved that it was not tuberculous in structure. In 1946 the eyelids were closed.

The patient was seen in the dermatology clinic of Mount Sinai Hospital for the first time in March, 1950. Solid whitish plaques and several denuded lesions were present on the buccal mucosae. Biopsy at that time of the superficial mucous membrane showed focal hyperkeratosis and large, flat, superficial intraepithelial bullae filled with edematous fluid, containing a few polymorphonuclear leucocytes and clumps of bacteria. There was dilation of superficial dermal

vessels with perivascular edema but minimal cellular infiltration. The diagnosis was that of a bullous mucosal lesion compatible with pemphigus vulgaris. A fragment from the oral mucosa also revealed leucoplakia. The Pels-Macht test gave a positive reaction for pemphigus on April 10, 1950. In November of that year the patient was admitted to the hospital with "canker sores" on the buccal mucosa, which went on to superficial ulceration. Some lesions were covered by a white pellicle.

In December, 1950, lesions appeared on the chin for the first time and were described as "diffuse erythema with scaling and crusting." These were diagnosed as factitious.

In January, 1952, the lesions of the oral cavity persisted but appeared more hypertrophic and were not ulcerated. On review of the history of corneal ulcerations and oral lesions, the possibility of Behcet's syndrome was considered. In May, 1952, the patient was admitted to the hospital with complaints of great soreness of the mouth, difficulty with mastication, inability to open the mouth, and occasional hemorrhage of the mucosa. Biopsy of a mucosal fragment showed chronic, nonspecific inflammatory infiltration beneath the epithelium. There was one small keratotic fragment. The patient has been followed in the clinic, and the lesions have remained static for the entire period described.

Treatment from March 15 to May 25, 1950, consisted in administration of 100 mg. of suramin sodium (Naphuride) intravenously three times a week, 2 cc. of crude liver extract intramuscularly twice a week, and 300 mg. of ascorbic acid daily.

In hospital, beginning Nov. 10, 1950, cortisone was applied as a mouth paint in a concentration of 25 mg. per cubic centimeter; chlortetracycline (aureomycin) was given, 250 mg., four times a day for one month, and use of multiple vitamins was prescribed.

In the outpatient department the patient was given various vitamins, crude liver extract, mouth washes, and general supportive therapy. One course of bismuth 1 cc. of the subsalicylate salt in oil three times a week for one month was given.

In hospital, in May, 1952, the patient received 25 mg. of corticotropin intravenously daily for one week; 500 mg. of oxytetracycline (terramycin) intravenously daily; 100 to 200 mg. of cortisone daily for two or three weeks, and 100,000 units of vitamin A intramuscularly.

On Jan. 5, 1953, an area 2.5 cm. in diameter was removed with the hot cautery and curette just at the angle of the mouth on the forward aspect of the mucosa of the right cheek.

The Wassermann reaction of the blood was repeatedly negative. All blood counts have been within normal limits, and all urinalyses have given normal findings. Blood chemistry determinations showed blood urea nitrogen to be 9 mg., fasting blood sugar 80 mg., calcium 10 mg., and sodium 144 mg., per 100 cc.; carbon dioxide-combining power was 53%, and total proteins measured 6.86 gm., with 4.08 gm. of albumin, and 2.78 gm. of globulin per 100 cc.

DISCUSSION

DR. GEORGE M. LEWIS: This case is a difficult one on which to formulate an opinion on the basis of one examination. Without a history I should make a diagnosis of leucoplakia, with the possibility of moniliasis or, as an outside chance, lupus erythematosus. We have to defer to Dr. Peck, who has studied this woman for so long and has good evidence that she has pemphigus. The lesions on the oral mucosa may be part of that disease. I know of no specific therapy to suggest, unless it be use of more vitamins in high dosage, especially the B complex.

DR. DAVID BLOOM: I should like to see a biopsy of the skin.

DR. ARTHUR W. GLICK (by invitation): This woman has been under psychiatric care for more than 10 years for a mixed psychoneurosis with masochistic tendencies. At one time it was felt that the ulcer on the eye was factitial. For 10 years she has been under continual care, with hundreds of visits and many hospital admissions for treatment by competent opthalmologists. At her last hospitalization, we saw her with the dermatitis of the chin, which we felt was self-induced. I can see no change in the lesions of the mucous membrane. If they were produced by some instrumentation, it must have been by constant rubbing of the mucosa. Perhaps everything would fit into that pattern. It is difficult, however, to visualize those oral lesions as being self-induced over a long time.

DR. LEONARD V. KORNBLEE (by invitation): It is amazing to think that these ulcers are self-induced lesions. It is one of the reasons that led us to use as drastic a procedure as

application of the hot cautery and curettage. We may not have gone deep enough, for the lesion returned quickly; but it seems we are dealing with something more than a factitial process.

DR. JOSEPH L. MORSE (by invitation): I am not sure what she has but do not think it is pemphigus. It surely is unusual to see lesions of pemphigus confined to the mouth for several years. The areas in the mouth resemble leucokeratosis rather than pemphigus. I am inclined to agree with the diagnosis of dermatitis factitia but have never seen self-induced lesions in the mouth like this.

DR. PAUL GROSS: I am inclined to agree with those who feel that the lesions in the mouth are primarily those of leucokeratosis and that the bullous changes are secondary. If there is any evidence of dyskeratosis in the microscopic sections, it would be worth while considering the diagnosis of Darier's disease. It is hard to conceive of the diagnosis of artifact on the bass of the clinical lesions and their location.

DR. ANTHONY C. CIPOLLARO: The clinical picture is most unusual, and the idea of a factitial eruption would never have occurred to me, but since Dr. Glick's explanation I am almost convinced that the condition is on a psychogenic basis. I can see how she could produce these lesions in the mouth by continual irritation with a liquid or by biting. It reminds me of flame swallowers who show thickening and coating on the tongue from continual trauma from flames.

DR. DAVID BLOOM: It seems to me that the combination of involvement of the eye and mouth is not coincidental, but of significance. This is a bullous eruption which does not represent the classic picture of fulminating pemphigus vulgaris, but which I think may nevertheless be classified under chronic pemphigus. As long as we have no definite criteria for pemphigus, this concept may be justified.

DR. ARTHUR W. GLICK (by invitation): People who have this type of neurosis, a masochistic, self-punitive approach to themselves, can be seen at night grinding their teeth constantly and rubbing their gums and teeth; so everything ties up—the ulcers that the ophthalmologists thought were factitial and the eruptions on the chin and in the mouth. I don't know anything else that would tie in with the whole story. On the uvula are two leucoplakic areas, and it is hard for me to see them as self-inflicted, although I can conceive of a hot rod being put there.

DR. ISADORE ROSEN: They extend pretty far down.

DR. ORLANDO CANIZARES: The patient has been hospitalized many times; it is difficult to believe that the patient could traumatize herself under close observation. Under hospital conditions it would be easier to determine whether the lesions are self-inflicted.

DR. ARTHUR W. GLICK (by invitation): When we first saw the eruption on the chin, there were linear scratch marks. We painted it with brilliant green and saw some staining under her finger nails, but we were not sure it was factitial.

DR. GEORGE M. LEWIS: Is there any case on record in which trauma has produced leucoplakia of as wide extent as this? If not, I think the traumatic theory could be thrown out. There is no history of traumatic insults.

DR. MAURICE J. COSTELLO: Did this patient have any synechiae? In essential shrinkage of the eyeball it is rather usual to see lesions on the hard and soft palate which persist indefinitely.

DR. LEONARD V. KORNBLEE (by invitation): May I ask Dr. Cipollaro what he would expect of thorium-x in such a case?

DR. ANTHONY C. CIPOLLARO: If this is leucoplakia, I doubt whether irradiation would do much good.

DR. DAVID BLOOM: I have seen phenobarital produce such lesions.

DR. SAMUEL M. PECK: When there is no explanation for a syndrome, it is easy to say it is psychogenic or self-inflicted. I believe this is neither. I have followed the patient for many years. The eyelids were closed up, and the ulcers went on underneath. No one who has experimented with trauma has been able to produce leucoplakia without an underlying predis-

position. These lesions do not look self-inflicted; they are superficial ulcers which seem to be part of a system, extending downward from the mouth, and they are not influenced by therapy. A traumatic lesion heals up rather quickly; these do not. It took months for a single lesion to heal. This condition is some sort of a process. The histology resembled that of pemphigus. The modified Pels-Macht test was positive. If it is moniliasis, it was uninfluenced by chlortetracycline, and we certainly did not find Candida.

Case for Diagnosis: Ectopic Nail Matrix? Presented by DR. GEORGE M. LEWIS.

Nonspecific Atrophic Lesions in a Half-Sister of a Patient with Typical Primary Macular Atrophy. Presented by DR. SAMUEL M. PECK.

Nummular Eczema Following Ecthyma. Presented by DR. SAMUEL M. PECK.

Lupus Miliaris Disseminatus Faciei. Presented by DR. NATHAN SOBEL.

Jack Wolf, M.D., President

George M. Lewis, M.D., Secretary

Feb. 10, 1953

Tinea Capitis (Trichophyton Tonsurans) of the Scalp in a Child. Presented by DR. MAURICE J. COSTELLO.

M. M., a white Puerto-Rican girl aged 4 years, presents an eruption limited to an area the size of a silver dollar on the left side of the scalp, which has been present for seven months. There are scales in the patches, which are thin and silvery in appearance, with minimal loss of hair. There is no fluorescence under the Wood light. Direct examination of a potassium hydroxide preparation revealed fungi. Culture on Sabouraud's medium revealed a velvety, cream-colored growth with a central depression. An older growth presented a crateriform design. Microscopic examination of the culture showed numerous microconidia along the side of the hyphae. Chlamydospores were found throughout the culture, with terminal swelling of the hyphae into club-shaped ends. Other children in the family are similarly affected. This is the type of fungous infection described by Pipkin (Pipkin, J. L.: Tinea Capitis in the Adult and Adolescent, A. M. A. ARCH. DERMAT. & SYPH. **66**:9 [July] 1952).

DISCUSSION

DR. GEORGE M. LEWIS: The incidence of this disease appears to be higher than formerly, although one wonders whether some cases have not been overlooked in the past. The disease may be endemic in Puerto Rico, since many of our cases occur among emigres from that country. The disease has also been observed in native citizens of the northern United States. Perhaps when one sees Puerto Ricans, one should examine the scalp, because the eruption is not often typical of the usual tinea capitis caused by Microsporum. One must not depend on examination with the Wood light and must be aware of the possible presence of the Trichophyton type. Clinically, this form of tinea capitis may closely resemble other diseases of the scalp, although the eruption is usually a little different from the condition that one might suspect. It may resemble psoriasis or seborrhea, but there is always a certain amount of alopecia. The proof is the finding of the organism in the hair and in cultural demonstration of the fungus.

DR. MAURICE J. COSTELLO: How about epilation in cases of this type?

DR. GEORGE M. LEWIS: This type of tinea capitis is hard to cure in any other way. Pipkin, who has had much experience, advises epilation and does not think any other therapy is effective. Others have reported a certain percentage of cures with topical therapy, but I think x-ray epilation is surest.

DR. ANTHONY C. CIPOLLARO: Dr. Lewis has covered most points. In cases in which there is any inflammation whatsoever the lesions clear up, either spontaneously or with topical remedies, but cases in which there is no inflammation, as in that of the girl I presented, who had had the infection for 14 years, the condition does not clear up until epilation is performed. The secret of success, even with epilation, is the removal of all stubbed hairs, which look

like black dots. It has to be done conscientiously and by the hour to effect a cure. I suspect there are many cases of this disease in New York that have not yet been detected, because the material does not fluoresce under the Wood light and some lesions are of the noninflammatory type. I should like to have a comment from Dr. Sobel regarding the public health aspects. Does he think these patients should be isolated? Should they be treated with the most effective methods; should they be allowed to go to school, or should they dilly-dally for years?

DR. ADRIAN BRODEY: From the public health point of view it is regrettable that this disease is not a reportable one. We have no way of knowing how prevalent it is.

DR. MAURICE J. COSTELLO: I am against having children with this infection returning to school before the infection is eradicated. If a child acquires impetigo or pediculosis capitis, he is removed. I must have seen five cases of tinea capitis due to this organism, and Dr. Lewis and Dr. Cipollaro have shown some. I am sure other members of this child's family have the infection, and before long there may be many cases. I think the Commissioner of Health should be told of it.

Basal-Cell Epithelioma in a Negro. Presented by DR. MAURICE J. COSTELLO.

M. E., a Negro woman aged 54, is presented from Bellevue Hospital with an eruption on the left buttock of five years' duration. The lesion is the size of a half-dollar, is ulcerated at various points, and has infiltrated hyperpigmented areas along its periphery. It has increased gradually in size during the past few years, and biopsy showed a typical basal-cell epithelioma. The patient is said to have had granuloma inguinale prior to the development of this lesion (Donovan bodies were found). The patient is presented because it is rare to see a basal-cell epithelioma in the Negro, and extremely rare to find it in a full-blooded Negro. This patient is not a full-blooded Negro. The lesion has occurred in an area of neurodermatitis which has been frequently scratched during these years. The biopsy tissue is available for study.

DISCUSSION

DR. ADRIAN BRODEY: It is interesting that this infrequent lesion in the Negro should be a pigmented basal-cell epithelioma. It is paradoxical that basal-cell epitheliomas are not pigmented oftener than they are, since melanoblasts are of basal-cell origin.

DR. NATHAN SOBEL: We have to accept the diagnosis of basal-cell epithelioma in this case. The finding of Donovan bodies in this case raises the question whether this organism is really the cause of granuloma inguinale or whether it is merely a saprophyte. I don't think it has been absolutely proved to be the cause, although most people accept it as the etiologic factor. In some cases in which granuloma inguinale persists for a long time, prickle-cell lesions develop. I should leave the question of granuloma inguinale in abeyance in this case.

DR. DAVID BLOOM: This patient is not a full-blooded Negro. The finding of a basal-cell epithelioma in such a patient is therefore not of as much significance as though she were a full-blooded Negro.

DR. ANTHONY C. CIPOLLARO: This location certainly is unusual, and the lesion is unusual for a basal-cell epithelioma. That is why I asked whether the histology is definitely that of basal-cell epithelioma, because other ulcerative lesions have to be considered. There was no definite pearly border, and I thought of Bowen's disease. However, since Dr. Sachs says the histology is definitely that of basal-cell epithelioma, I accept that diagnosis.

DR. MAURICE J. COSTELLO: I do not think the patient had granuloma inguinale, because after any length of time she would have had more sequelae, such as hyperpigmentation and hypopigmentation and scarring, which she does not show. The lesion might even suggest granuloma to a person seeing it in a Negro. I have never seen basal-cell epitheliomas in a woman of such dark coloring; so it is still rare. It occurs in an area of neurodermatitis; the opposite buttock shows linear excoriations.

Pemphigus Vulgaris Complicated by Diabetes, Treated with Corticotropin and Cortisone. Presented by DR. DAVID BLOOM (previously presented April 8, 1952).

L. F., a woman aged 54, was seen for the first time at the Skin and Cancer Unit with a bullous eruption of two months' duration. The lesions, located on the chest and face, consisted of hazelnut- to lemon-sized tense, but mostly flaccid, bullae, many of which were hemorrhagic. There were several lesions in the mouth. During four months of observation at that institution the eruption gradually extended to the extremities, groins, and vulva, and many denuded areas developed.

Laboratory examinations, including urinalysis, blood counts, blood chemistry determinations, and serologic tests for syphilis, all gave normal results. Biopsy was reported on one occasion as showing pemphigus vulgaris and on another as revealing dermatitis herpetiformis.

The patient, who had previously refused hospitalization, became weaker and unable to attend to her work and entered Sydenham Hospital on Dec. 13, 1951. Laboratory examinations then revealed glycosuria and an increased glucose content of the blood. She then gave a history of glycosuria in 1944 and of a recurrence following an automobile accident in 1945, at which time she had received insulin.

In spite of her diabetes, which was treated with dietary measures and insulin, corticotropin was given intramuscularly, 25 mg. twice a day. This dose was gradually increased over a period of 24 days to 110 mg. daily, which was sufficient to keep her free from the eruption. The bullae healed, leaving darkly pigmented plaques. In order that the adequate amount of oral cortisone might be established, administration of this hormone was started at a dose of 400 mg. daily and gradually reduced to 125 mg. over a period of 18 days. At this dosage new bullae began to appear. The dose was therefore gradually increased to 200 mg., which was sufficient to keep the patient free of lesions. With increase in the dose of corticotropin and cortisone, the insulin also had to be increased. Frequent blood sugar determinations and electrocardiographic recordings were made.

While the patient was under hormonal therapy, hirsutism, moon facies, a hump on the upper part of the back, and striae on the trunk developed. On one occasion the systolic blood pressure rose from 125 to 160 mm., but several days later it returned to a lower level. During several days of her hospitalization the patient became extremely irritable, but this condition subsided. She was discharged on Feb. 13, 1952, after a stay of two months, and returned to her work as telephone operator. After her discharge she took cortisone orally, was on a salt-free diet, received 3 gm. of potassium chloride and 48 units of insulin daily, and visited the diabetes and the dermatology departments of University Hospital regularly once a week. The cortisone was gradually and cautiously reduced, and its use was finally discontinued 16 weeks prior to the time of this report. In spite of this, the patient has been entirely free of lesions, complaining only of occasional pruritus. Her diabetic condition has also improved, for the urine is sugar-free and the blood sugar determination shows normal values.

DISCUSSION

DR. DAVID BLOOM: The fact that this patient is well, although she has been without cortisone therapy for four months, is a hopeful sign that she may not need further treatment. The statement that she is well must be qualified by the fact that she has an occasional bulla, which dries up quickly. In the case of this patient, who exhibited psychotic symptoms during treatment, particularly because of her diabetes, I believe the only rational procedure is to keep her under observation without administration of cortisone.

Systemic Disseminated Lupus Erythematosus. Presented by DR. NATHAN SOBEL.

Case for Diagnosis: Mycosis Fungoides? Reticulum-Cell Sarcoma? Presented by DR. WILBERT SACHS.

Cirsoid Aneurysm in the Left Ear. Presented by DR. MAURICE J. COSTELLO.

Lichen Planus in a 5-Year-Old Child. Presented by DR. NATHAN SOBEL.

Linear Nevus and Lichen Simplex Chronicus Localized in Adjoining Dermatomes. Presented by DR. PAUL GROSS.

Case for Diagnosis: Dermatitis Factitia? Presented by DR. PERRY M. SACHS.

Keloids. Presented by DR. JACK WOLF.

Hyperkeratotic Lupus Erythematosus. Presented by DR. DAVID BLOOM.

Case for Diagnosis: Kaposi's Sarcoma? Presented by DR. ORLANDO CANIZARES.

METROPOLITAN DERMATOLOGICAL SOCIETY OF LOS ANGELES

Harold C. Fishman, M.D., *President*
Stanton B. May, M.D., *Vice-President*
Fred F. Feldman, M.D., *Secretary*

Nov. 25, 1952

Parapsoriasis en Plaque. Presented by DR. MAX POPPER.

L. G. W. is a 7-year-old white boy, born in the United States, whose past history is noncontributory to his present illness. The skin changes consist of a number of plaques, irregularly distributed over the skin, with only slight tendency toward symmetrical localization. The first of these lesions appeared two years ago on the dorsum of the left foot. Other plaques developed later on the abdomen, legs, and a wrist. The patches are almost level with the skin, are round, and have a sharp and irregular border, which is slightly elevated peripherally. The lesions vary from 2 to ½ in. (5 to 1.3 cm.) in diameter and are sepia brown; the surface is smooth and not scaly. The lesions are not pruritic.

Biopsy findings indicate marked and uniform hyperkeratosis, with occasional hyperkeratotic plugging of follicles. There is no parakeratosis. The granular layer, preserved throughout, is irregular in thickness and is edematous in spots. Globular bodies of agglomerated edematous granular cells, "mole hills" of edematous granular cells, which have been found to occur rather frequently in different types of parapsoriasis are present. (For comparison, slides are shown from a case of pityriasis lichenoides chronica which as presented before this society on April 25, 1950.) The papillae are partly obliterated, and there is a tendency toward flattening of the epidermodermis junction. There is marked infiltrate of round cells in the midcutis surrounding dilated vessels.

Treatment, consisting of repeated irradiation with ultraviolet light, did not produce any change in the lesions.

DISCUSSION

DR. MEYER BERKE: I thought that a few of the lesions on the back of the hand were separate and smaller papules and that they were in many ways suggestive of granuloma annulare. I did not think that the slide was inconsistent with the histologic picture of granuloma annulare.

DR. LAWRENCE UNDERWOOD: I, too, thought that the clinical picture was not that of parapsoriasis. Clinically, I favored granuloma annulare, with a second consideration being erythema elevatum diutinum. Histopathologically, however, it was not diagnostic for these conditions.

DR. EDWARD L. MURPHY: I agree with the diagnosis of granuloma annulare. In a boy of 7 years of age granuloma annulare is fairly common, but parapsoriasis en plaque would be a very unusual skin disorder.

DR. FRED F. FELDMAN: The two diagnoses that I considered here were granuloma annulare and erythema perstans. I feel that the histologic picture did not conform to granuloma annulare but possibly did to erythema perstans. I, too, have never seen a case of parapsoriasis en plaque with this particular clinical picture, but I am sure that Dr. Popper must have some definite reasons for calling this a case of parapsoriasis en plaque.

DR. ROSE B. SAPERSTEIN: If one interprets this pathologic picture as parapsoriasis and if the clinical picture is so unlike parapsoriasis, I think I should have liked to have another biopsy done.

DR. STANTON B. MAY: I should like to ask Dr. Popper, if he considers the histopathology of parapsoriasis en plaque characteristic. I have always felt that one could not diagnose parapsoriasis solely on the basis of the microscopic findings.

DR. MAX POPPER: I anticipated a great deal of disagreement with the diagnosis as presented by me. The diagnoses offered in the discussion have been carefully considered. My first clinical impression was erythema elevatum diutinum. Diagnoses of granuloma annulare, some of the rare erythemas, as erythema figuratum perstans (Wende), macul anesthetic leprosy, and

mycosis fungoides had to be ruled out. The diagnosis of parapsoriasis en plaque disseminées was based on the fact that the clinical picture is compatible with this disease and that its histological picture is much closer to the classic description of parapsoriasis en plaque than to that of any of the other diseases mentioned here. Specifically, I have not found any evidence of granuloma annulare in the histological sections.

The histology of this type of parapsoriasis is characterized by a rather remarkable infiltrate in the cutis. As Fritz Juliusberg has pointed out in his monograph on parapsoriasis (Handbuch der haut- und Geschlechtskrankheiten, Vol. 7, pt. 1, p. 333), "The considerable end dense infiltrate in the cutis seems to be in contradiction to the fact that no infiltrate can be palpated clinically." Another quite characteristic feature is an edema which is more pronounced in the granular layer than in the Malpighian layer. On other occasions I have also pointed out a particular peculiarity of the granular layer; it is irregular—irregular in size and also irregular in that some of the granular cells seem to be quite edematous, while in other sites the granular layer appears to be quite normal. In the present slides I tried to demonstrate the so-called "mole hills"—globular bodies of edematous granular cells. Irregularities of the granular layer and the presence of these globular bodies are not diagnostic for parapsoriasis, but they occur very commonly in this type of lesion.

I agree with Dr. Murphy that this disease is rare in children; in most cases the disease develops between the ages of 15 and 25. However, Riecke found in 30 collected cases the age incidence to be between 5 and 30. (Riecke, E.: Lehrbuch der Haut- und Geschlechtskrankheiten, Ed. 7, 1922, Vol. 7, p. 182.)

The color of the lesions, sepia, is also not uncommon in this disease—so much so that a synonym of this condition is xanthoerythroderma perstans (Radcliffe Crocker).

The histological picture as presented does not bear out the clinical impression of skin conditions which had to be considered in the differential diagnosis. Therefore the diagnosis of these diseases had to be discarded.

Localized Myxedema (Pretibial). Presented by DR. LAWRENCE J. UNDERWOOD.
Granuloma Annulare; Necrobiosis Lipoidica? Presented by DR. DAVID N. ALCON.
Case for Diagnosis (Insect Bites? Dermatitis Herpetiformis?). Presented by DR. STANTON B. MAY.
Acne Varioliforms? Presented by DR. IRVING A. LEWE.
Creeping Eruption (Larva Migrans). Presented by DR. MEYER BERKE.
Systemic Lupus Erythematosus (Follow-Up). Presented by DR. STANTON B. MAY.
Scleroderma with Hyperpigmentations. Presented by DR. WILLARD L. MARMELZAT for suggestion for therapy.

NEW ENGLAND DERMATOLOGICAL SOCIETY

Mildred Ryan, M.D., *President*

Joseph Goodman, M.D., *Secretary*

Oct. 8, 1952

Primary Inoculation Tuberculosis and Erythema Nodosum. Presented by DR. LEON BABALIAN and (by invitation) DR. JOSEPH PORTER and DR. GISELA DAVIDSON.

B. C., a 19-year-old white student nurse, pricked her right palm with a needle which had been used for aspiration of a tuberculous abscess. The lesion produced by the injury healed within a few days. Three weeks after the injury, redness and swelling, followed by oozing, appeared at the site of the injury, and tender enlarged lymph nodes appeared in the right epitrochlear area. Within a few days fever appeared, and it continued to appear each evening for two months. Two months after the injury, an eruption consisting of erythematous tender areas appeared on the anterior aspect of the legs, the chest, and the back.

Repeated chest x-rays, both before and after the accident, were negative. A tuberculin patch test was negative before the accident and became positive two months after the accident. Biopsy of a lesion on the leg showed chronic inflammation. Biopsy of a lymph node showed changes consistent with tuberculosis, with numerous acid-fast bacilli. Inoculation of animals with material from the erythema nodosum lesions failed to give a positive result.

DISCUSSION

DR. FRANCIS P. MCCARTHY, Boston: It is very difficult to get positive results from the inoculation of guinea pigs with material taken from erythema nodosum lesions, even when the tuberculous origin is unmistakable, as in the present case. The organisms may be absent or so few may be present that the result of the animal inoculation is negative.

Essential Hyperlipemia with Xanthomatosis. Presented by DR. CHESTER N. FRAZIER, Boston.

R. V., a 42-year-old white man, had had angina pectoris for four years. During these four years, yellowish nodules had appeared on the extensor aspect of the elbows and knees, the buttocks, the calves, and the ankles and feet. There was no family history of similar lesions. Biopsy showed changes consistent with xanthoma tuberosum.

A diet containing 10 gm. of fat per day was prescribed. During four months of this diet, there was a weight loss of 28 lbs. (12.7 kg.). At the same time, there was about 60% involution of the skin lesions. The symptoms of angina pectoris also disappeared.

Lipid studies of the blood revealed a turbidity of 31.7 units before the period of low-fat diet and 8.4 units after the period of low-fat diet. Blood chemistry studies gave the following values.

	Before, Mg. per 100 Cc.	After, Mg. per 100 Cc.
Total cholesterol	1,000	340
Cholesterol esters	537	200
Phospholipids	1,110	560
Total fatty acids	4,040	1,690
Calculated neutral fats	3,005	...

DISCUSSION

DR. EDWIN O. WHEELER, Boston (by invitation): I have been interested in patients with various disturbances of liver metabolism because of the possible relationship of these disturbances to coronary diseases. In the past few months, we have seen a number of patients with essential xanthomatosis with attendant nodules and coronary disease. The literature has tended to lead one to believe that in patients with hyperlipemia, in contrast to patients with essential hypercholesteremic xanthomatosis, coronary disease does not develop. However, of the six patients that I have seen with hyperlipemia recently, two had coronary disease beginning in their fourth decade. I feel that it is very probable that in patients with this disorder, as well as in those with essential hypercholesteremic xanthomatosis, xanthomatosis of the coronary vessels may develop.

DR. WALTER F. LEVER, Boston: This patient has had an impressive response to dietary regulation, particularly when one considers that the diet was not carried out by the hospital but by the patient himself at home. I should like to ask Dr. Wheeler what the general results of the low-fat diet are in primary hyperlipemia and how these results compare with those in primary familial xanthomatosis.

DR. EDWIN O. WHEELER, Boston (by invitation): This is the only patient with primary hyperlipemia whom I have succeeded in keeping on a low-fat diet, and so results are limited to this one case. However, I have four patients with essential hypercholesteremic xanthomatosis and coronary disease who have followed a diet containing less than 25 gm. of fat for a year or more. Those patients had a statistically significant fall in cholesterol, never to normal levels, usually to levels of around 300. However, the nodules continued to progress, and the patients continued to have angina pectoris. Therefore, the results in the essential familial xanthomatosis were not as striking as those found in his patient with essential hyperlipemia.

DR. WALTER F. LEVER, Boston: I should like to emphasize the importance of distinguishing between these diseases. There is a difference in the appearance of the blood serum in primary hyperlipemia and in essential familial xanthomatosis. In the former, the serum is milky; in the latter, it is clear.

The opinion is generally held that in patients with essential familial xanthomatosis cardiovascular disease often develops at a relatively early age. It is also the general opinion that primary hyperlipemia is usually not accompanied by cardiovascular disease. In my experience, both conditions are accompanied by cardiovascular disease.

Cardiovascular Syphilis, Chronic Discoid Lupus Erythematosus. Presented by DR. BERNARD APPEL, Lynn, Mass.

Pityriasis Rubra Pilaris. Presented by DR. JACOB H. SWARTZ, Boston.

Sclerosing Basal-Cell Epithelioma. Presented by DR. WALTER F. LEVER, Boston and DR. MERLE A. HAANES, Beverly, Mass.

Poikiloderma Vasculare Atrophicans? Majocchi's Disease? Angioma Serpinginosum? Presented by DR. LEO KORETSKY, West Medford, Mass.

Tertiary Syphilis of the Skin. Presented by DR. BERNARD APPEL, Lynn, Mass.

Chronic X-ray Dermatitis. Presented by DR. FRANCIS M. THURMON, Boston.

Psychogenic Alopecia? Presented by DR. BERNARD APPEL, Lynn, Mass.

Mycosis Fungoides? Presented by DR. CHESTER N. FRAZIER, Boston.

Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi. Presented by DR. CHESTER N. FRAZIER, Boston.

Hairy Black Tongue. Presented by DR. JULIUS PICARD, Fall River, Mass.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

Marion H. Sulzberger, M.D., Chairman

J. Lowry Miller, M.D., Secretary

Sept. 30, 1952

Lupus Erythematosus (Treated with Quinacrine Hydrochloride [Atabrine Dihydrochloride]). Presented by DR. GEORGE M. LEWIS, for DR. DONALD BROOKING.

M. M., a 46-year-old white housewife, was first seen on Aug. 21, 1951. She stated that approximately two years previously she had noted the presence of a red pea-sized nodule just below the bridge of her nose. The lesion persisted and would become aggravated upon exposure to sunlight. The patient was treated for several months with liver injections, penicillin injections, oral sulfonamide tablets, and vitamin B_{12}. There was little change in the skin lesion. The patient also complained of dizziness, weakness, and fever. Later, she was given a short course of bismuth injections, but these were discontinued when she complained of pain. Shortly before she was seen in the skin clinic, a swelling of the left knee joint developed which was diagnosed as arthritis and treated with salicylates.

The personal history is noncontributory, except that the patient thought that she sunburned easily.

Physical examination revealed the following findings: Over the bridge of the nose there was a rather sharply demarcated slightly elevated irregularly shaped erythematous plaque 15 by 20 mm. in greatest diameter. The lesion felt edematous on palpation. There were tiny telangiectases over the lesion. There was no scale and no gross atrophy. Distal to this lesion, there was a second similar lesion, 10 by 10 mm. The rest of the history was noncontributory, except for a temperature of 37.4 C.

Laboratory tests revealed the following findings: Results of repeated urinalyses have been negative, except for a low specific gravity. Numerous blood tests have shown the following results: hemoglobin content, 12.9 to 14.2 gm.; red blood cells, 4,200,000 to 4,800,000; white blood cells, 5,500 to 11,000 per cu. mm. (lymphocytes, 15 to 37%); blood urea nitrogen, 19 mg.; blood protein, 7.8 gm.; albumin-globulin ratio, 5.3/2.5. The sedimentation rates were as follows: Aug. 23, 1951, 18 mm.; Oct. 10, 23 mm.; Oct. 17, 17 mm.; Oct. 24, 23 mm.; Oct. 31, 27 mm.; Nov. 7, 24 mm., and April 23, 1952, 21 mm. A roentgenogram of the chest showed a normal picture.

The findings of the microscopic examination were as follows: There was keratotic plugging of the follicles, and the epidermis was thin and flat. There was marked basophilic degeneration in the upper cutis, and considerable edema was in evidence. Inflammatory infiltration was in evidence. The inflammatory infiltration was composed of lymphocytes, and there was invasion of the basal-cell margins of the follicles only.

The pathologic diagnosis was lupus erythematosus.

From Sept. 14, 1951, to July 2, 1952, the patient received oral Tofaxin (vitamin E preparation) 100 mg. three times a day, parenteral Tofaxin 1 cc. weekly, Lextron (a liver-stomach extract with iron) capsules, and vitamin B complex, in addition to local CO_2 therapy. During this period, the lesions would improve temporarily after the CO_2 therapy. Her oral temperature varied between 37 and 37.6 C. (98.6 and 99.7 F.). On June 18, 1952, quinacrine hydrochloride (Atabrine Dihydrochloride) therapy was started, 100 mg. daily to July 26, and then 100 mg. three times a day until Aug. 27, then 100 mg. daily up to the present. By July 2, the patient's skin had assumed a general yellow hue, and the original lesions had almost entirely faded.

DISCUSSION

DR. DAVID BLOOM: In one case of subacute lupus erythematosus in a young girl there was no response to quinacrine. However, I was impressed with the prompt effect of quinacrine in a dose of 200 mg. a day in a case of a young woman with discoid lupus erythematosus which for several years had been resistant to all kinds of therapy.

DR. MARION B. SULZBERGER: This is a method of treatment which I believe was introduced by Francis Page of England. An abstract of Page's article was included in "The 1951 Yearbook of Dermatology and Syphilology," page 103. I have had the opportunity to speak to many people who have used this method and their results have been good everywhere. I spoke to Dr. Livingood, Dr. Haserick, Dr. Pillsbury, and Dr. Rothman in this country, and to several investigators in England. These investigators have together treated more than 100 patients. We ourselves have between 40 and 50 cases at the Skin and Cancer Unit, and the results indicate that this treatment is one of the best, if not the best, for chronic discoid lupus erythematosus. Of course, the question arises: Will quinacrine therapy be good and, if so, how good will it be in acute disseminated lupus erythematosus? There the opinions that I have received have not been so unanimous. Two patients with acute disseminated lupus erythematosus who were treated in Philadelphia have been doing very well. Haserick has treated one patient, with failure. In all these acute cases the treatment has, of course, been combined with cortisone.

There have already been cases of lichenoid quinacrine dermatitis in lupus erythematosus in which there was treatment in temperate climes with quinacrine (Tillman and associates).

DR. HERMAN GOODMAN: How does it work?

DR. GEORGE M. LEWIS: In the cases in which there has been treatment by us with quinacrine it is almost always necessary to induce a yellow coloration of the skin before a satisfactory therapeutic effect is obtained. It is important that the patients be told to expect the yellowing; otherwise they will be surprised. It is interesting that the patients invariably accept the yellow coloration in preference to the disease, whereas in some cases in which the disease is mild I should have thought otherwise. Toxic effects of the drug must be kept in mind. It is curious that all drugs effective in the treatment of lupus erythematosus often produce toxic side-reactions. Quinacrine hydrochloride (Atabrine Dihydrochloride) seems to have the least harmful effect on a percentage basis. Quinacrine therapy may have to be continued over a long period, and if the drug is discontinued the relapse may be prompt.

Adrenogenital Syndrome. Hyperhidrosis of Hands and Feet. Presented by DR. DOUGLAS TORRE, for DR. HERBERT SPOOR.

P. F., a 3½-year-old white boy, with adrenogenital syndrome and adrenal insufficiency, has been regulated at New York Hospital since infancy. During this period there have been seven hospital admissions for control of upper and lower respiratory infections and for one of the childhood exanthemas (measles).

Control of the metabolic condition has been satisfactory. At present he is being given cortisone and desoxycorticosterone (Doca), and there is a strict regulation of salt intake. Of the dermatological conditions, the hyperhidrosis has existed since birth, the hyperkeratosis since 9 months of age, and the comedo acne for the past six months.

Both hands and feet have shown a pronounced hyperhidrosis and hyperkeratosis, with much maceration and apparent infection. With therapy there has been great improvement during the past two months. The comedo, acneform lesions of the forehead have decreased in number and size since a hexachlorophene (G-11) soap-cleaning routine was adopted.

The most recent reported blood studies showed the following findings: urea nitrogen, 13.5 mg. per 100 cc.; NaCl, 96.0 mg.; sodium, 135.6 mg.; CO_2 concentration 27.09 vol.%; protein, 6.7 gm., and potassium, 4.35 mg.

Urinary 17-ketosteroids are maintained under 7 mg. every 24 hours and have ranged from 1.7 through 3.0 to 7 mg.

The blood pressure is 130/70; the height is 113 cm. and the weight 21.9 kg.

Mycological studies of the hands and feet have shown negative results on several occasions. The first cultures taken showed a late growth of Candida, which is considered of secondary significance.

The hands and feet have had daily administrations of 0.1% dilute formalin for six weeks, and good improvement is shown. Methantheline (Banthine) bromide therapy was considered, but was advised against on metabolic grounds.

DISCUSSION

DR. CARL TRUMAN NELSON: I did not know that hyperhidrosis and keratosis of the palms and soles were part of the adrenogenital syndrome.

DR. PAUL GROSS: The clinical picture of the skin condition is suggestive of a keratoma palmare and plantare hereditarium. The history is compatible with this diagnosis, since we know that the first signs of this disease are hyperhidrosis and erythema of the palms. The keratoderma may develop gradually.

DR. DAVID BLOOM: I believe that the child has keratoderma palmare et plantare, which is independent of the adrenogenital syndrome. I wish to ask the presenter about the hypertension of the child, which is a sign of hyperadrenalism and not of adrenal insufficiency.

DR. DOUGLAS TORRE: This patient at this time does not present a pure picture of his adrenogenital syndrome because he is being treated with cortisone. Some of the acne of the face which he presents is probably due—at least in part—to the cortisone therapy.

DR. MARION B. SULZBERGER: Do you know what his blood pressure was before the start of cortisone therapy?

DR. HERBERT SPOOR: His blood pressure varies. The one that is recorded is the highest one that has been detected recently. The blood pressure is not, in the opinion of the pediatricians, an indication of the adrenal status. It indicates the state of the well-being of the body, because with the adrenal insufficiency, which is characteristic of the syndrome, the blood pressure is very low. With adequate therapy—in this case, cortisone therapy—the blood pressure rises to a level which is compatible with good existence. It is a little higher in this patient than it should be for proper maintenance, according to the pediatricians.

DR. FRANCES PASCHER: I noted some findings that fit in with an Ehlers-Danlos syndrome in this case. There is some hyperextensibility of the interphalangeal and wrist joints, and the skin of the forearms has a rubbery, doughy feel. These findings are rather interesting in view of a similar case of Ehlers-Danlos syndrome combined with the adrenogenital syndrome in a 5-year-old girl, who was presented at the Bronx Dermatological Society on Feb. 21, 1952. Recent work in requiring confirmation (Ehlers-Danlos Syndrome: Report of a Case with Suggestion of a Possible Causal Mechanism, *A. M. A. Am. J. Dis. Child.* **83**:197, 1952) indicates that the Ehlers-Danlos syndrome may be due to prolonged hyperadrenocorticism, as in the Cushing syndrome.

Lupus Vulgaris. Presented by DR. CHARLES SHEARD.

F. O., a white man, aged 53, had always been in good general health. There is no tuberculosis in the family, and he has never been exposed to the disease.

The present condition began as a small patch on the vertex of the scalp, in early childhood. Some time after, but before the age of 6, left posterior cervical adenopathy developed, and skin lesions soon appeared in the overlying area. The process gradually spread over the back and left side of the neck and the lobule of the left ear. The right anterolateral side of the neck became involved some two years ago.

The patient was first seen eight months ago, at which time typical lupus vulgaris was present in the above-mentioned areas. The involved skin was diffusely red, with many apple-jelly nodules.

Physical examination revealed minimal erythema of the ear lobe.

Isoniazid (isonicotinic acid hydrazide, Nydrazid) therapy, 100 mg. two times a day, was begun 4½ months ago and has been continued to date. The lesions have almost completely involuted with therapy.

DISCUSSION

DR. DAVID BLOOM: Has any flare-up reaction in the lesion been noted in the course of therapy? In one patient with lupus vulgaris whom we treated with isoniazid (Rimifon) a marked erythematous reaction in the lesion developed several times. The end-result of treatment in that patient was very satisfactory.

DR. MORRIS LEIDER: The patient of Dr. Bloom is a middle-aged woman, a native of Italy, who had suffered from lupus vulgaris for a score of years. The process involved the left side of the face, from the hair line to the angle of the jaw. The area of involvement was always superficially ulcerated, and by the time of the institution of our treatment, the entire pinna of the left ear was gone. Isoniazid (Rimifon) was administered under hospital conditions for about three months in doses of 2 to 4 mg. per kilogram a day. During this treatment the tuberculous process seemed on several occasions to flare in a manner suggesting the Jarisch-Herxheimer reaction and then to subside, although treatment was never discontinued. The patient was reexamined just the other day, which is several months after cessation of treatment, and I would say that she is cured. She now shows a flat, smooth, pliant scar, which merges imperceptibly with the normal skin. The appearance is so good that she is being courted and will shortly be married.

DR. MARION B. SULZBERGER: Did you want to say anything about the general results in other cases and other diseases?

DR. MORRIS LEIDER: Dr. Sawicky at the Skin and Cancer Unit has treated about a half-dozen patients with lupus vulgaris with both isoniazid (Rimifon) and an isopropyl derivative of isoniazid (Marsilid). In some there was an initial response, but nothing dramatic and nothing sustained. We at Bellevue have also used isoniazid in two cases of Bazin's tuberculoderm, one case of scrofuloderma, two cases of leprosy, and two cases of sarcoidosis. Scrofuloderma and erythema induratum seem to be favorably affected; lepromatous leprosy seems to benefit, but sarcoidosis does not. Lupus erythematosus does not respond favorably. If one may be permitted a preliminary conclusion I would say that isoniazid seems to be of some effect in those forms of mycobacterial infections that are bacilli laden.

DR. CARL TRUMAN NELSON: We have not had a case of lupus vulgaris to treat with isoniazid (Nydrazid) or with one of the other isoniazid derivatives. In the patients we have treated, we have not noticed any Jarisch-Herxheimer effect on institution of therapy. In fact, in one of our patients with leprosy the initial response to isoniazid was phenomenally good for 10 days or so. There was a prompt clinical improvement in the skin lesions, even though there were about as many bacilli as there had been before treatment was begun.

Trichophyton Purpureum Infection (Generalized). Presented by DR. GEORGE M. LEWIS, for DR. HERBERT SPOOR.

D. N., an 8-year-old boy, has scaly erythematous gyrate lesions of the trunk, face, neck, scalp, and extremities. These have been diagnosed as tinea and treated topically with many agents during the past four years. None of the lesions have been cured, but have often shown temporary improvement.

Physical examination revealed the following findings: The scalp shows diffuse erythema with associated patchy alopecia. There are lichenified plaques scattered over the entire body. The infection is present on both the hands and the feet, but it is of particular note that the nails are not involved.

Skin scrapings and cultures have been made from lesions on the body, face, scalp, and extremities several times since the patient was first seen, in July, 1948. Trichophyton purpureum has been found from all types of lesions.

The trichophytin test showed only a mild immediate wheal reaction, with a negative reaction in 48 hours.

The following topical agents have been used therapeutically: Mazon (ointment containing mercury, salicylate, benzoic acid, salicylic acid, and tars), resorcinol (Resorcin), iodochlor-

hydroxyquin (Vioform), benzalkonium chloride (Zephiran), ammoniated mercury, carbol-fuchsin paint (Castellani's Paint), zincundecate (Desenex), Asterol (2-dimethylamino-6-[beta-diethylaminoethoxy]-benzothiazole dihydrochloride), nitromersol (Metaphen), salicylaniolide, sodium thiosulfate, and sulfur and salicylic ointment.

DR. GEORGE M. LEWIS: There is an important question that I should like to ask. Does anyone in the section feel that this boy should go to school and mix with other children?

DR. BEATRICE M. KESTEN: It seen to me that a school nurse could aply the therapy and permit the children to attend school. Children with ringworm of the scalp could wear the bunny caps at all times and need not be segregated. After all, how harmful is the ordinary ringworm of the scalp anyway?

DR. ARTHUR BERNARD HYMAN: A few years ago a questionnaire was sent around as to the familial and marital infection in dermatophytosis. I do not think that there is any statistical material relating to infection in the case of T. purpureum, but as far as we can judge from clinical cases, infection with T. purpureum from one member of the family to another is very rare, and it is probably safe to let that child go back to school. I do not know of any cases or records of any cases of conjugal or familial T. purpureum infection. It must be very rare, if it does exist.

DR. GEORGE M. LEWIS: Provision has been made for home instruction for this child. I am not sure whether the child is shy or is mentally deficient. It would be my feeling that the disease is mildly contagious, and that if he attends school there is a certain danger to other children. The problem here is more difficult than with tinea capitis due to Microsporum audouini, since the rash due to T. purpureum defies rapid cure and in many instances may persist for many years.

DR. MARION B. SULZBERGER: Have you seen, or do you know of reports of, familial cases of T. purpureum?

DR. GEORGE M. LEWIS: If you examine carefully the wife or husband of a patient with T. purpureum infection you will often find that he or she is also infected.

DR. MARION B. SULZBERGER: You think that active infection in conjugal partners is common?

DR. GEORGE M. LEWIS: I do not know what you mean by "active." Do you mean inflammatory?

DR. MARION B. SULZBERGER: Yes.

DR. GEORGE M. LEWIS: That is uncommon, since, in general, the inflammatory response to this organism is rare.

DR. MARION B. SULZBERGER: I think that too; one might discover fungi, but the infection is quiescent.

DR. GEORGE M. LEWIS: Then it is a matter of definition. In one person it may be more extensive and in another it may be limited.

Case for Diagnosis: Sarcoid? Granuloma Annulare? Panniculitis? Presented by DR. ANTHONY CIPOLLAR, for DR. HERBERT SPOOR.

Erythema Multiforme (Toxic) (Due to Cancer?). Presented by DR. J. LARRALDE and DR. E. L. WORTHINGTON (by invitation).

RHODE ISLAND DERMATOLOGICAL SOCIETY

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Feb. 16, 1953

Melanomata Pathologically Malignant, Clinically Nonmalignant, in a Case of Xeroderma Pigmentosum. Presented by DR. F. RONCHESE, Providence.

A woman aged 35, with xeroderma pigmentosum since the age of 2 years, was the subject of a paper presented at a meeting of the New England Cancer Society, in Providence, Nov. 6, 1946 (*Rhode Island M. J.* **30**:225 [April] 1947).

Fig. 1.—Xeroderma pigmentosum in a patient aged 25, taken in 1942, when a pathologically malignant melanoma (arrow) was removed.

The areas chiefly involved are, as usual, the exposed ones—the face, neck, upper portion of the chest, arms, and, lower legs. The condition, which has become progressively worse in the last 20 years, has nonetheless not prevented normal housework on a farm and marriage, five years ago, thus far childless. An older sister, living in a neighboring city, has a milder form of xeroderma pigmentosum, but with the same pattern of spotty hyperpigmentation on the exposed parts. Many of the lesions were widely surgically excised and diagnosed as malignant melanomas "of unknown origin." The two sisters are the only ones affected among nine children.

Fig. 2.—Appearance when the patient was presented on Feb. 13, 1953, showing the types of pathologically malignant melanomas, treated as common moles and healing with a satisfactory soft, white scar and no sign of local or distant recurrence in 10 or more years. The patient is 35 and in apparent good health.

The patient was seen first in 1942. She desired to have a 5 by 2 by 3 in. (12.5 by 5 by 7.5 cm.), sausage-shaped subcutaneous tumor removed from her left lower leg. Pathologically, this tumor was malignant melanoma (Dr. B. E. Clarke). The face and chest had dozens of basal-cell epitheliomata, from 2 to 5 or 10 mm. in diameter. They were too numerous for surgical removal, and irradiation was contraindicated. They were removed by electrocoagulation, as is done for common moles, with a smooth, white scar as a result. Intermingled with telangectases, the basal-cell epitheliomata, and the keratoses (viz., areas having the typical appearance of a senile or solar or irradiated skin) were innumerable spots of hyperpigmentation of all shades, from light brown to ink-black.

On the arms and lower legs, tumors, fungating, bleeding, ink-black, raised 1 or 2 cm. on the surface of the skin, and 1 or 2 cm. in diameter, demanded some form of therapy. There were so many that wide surgical excision was impracticable. Some were surgically removed—some with the biopsy punch and some by electrocoagulation, like common moles. When the dressing was changed, the surface was seen to be covered with material looking like black soot. All areas healed in a few weeks, with a smooth, soft white scar, and there has been no sign of local recurrence or metastasis in the past 15 years. The pathological diagnosis was malignant melanoma (Dr. H. Fanger, Dr. P. Catinella, and Dr. S. W. Becker).

When a lesion is diagnosed as malignant melanoma, it is usually widely excised, and all possible parts are removed. The patient usually recovers. In such cases, it is impossible not to think of the possibility of a clinically nonmalignant lesion. Next one naturally asks: How often is a pathologically malignant melanoma clinically nonmalignant? Then, Is extensive surgery an absolute indication after a pathological report of malignant melanoma? Should the melanoma of Xeroderma pigmentosum, healing with a form of treatment generally employed for nonmalignant lesions, be considered a separate entity? As long as there is a malignant xeroderma pigmentosum (Froboese, C.; Über das Xeroderma pigmentosum blastomatosum malignum, Gaz. méd. port. **4**:593, 1951), could there not also exist a benign form of the disease? How can one diagnose the condition as benign when pathological reports are of high malignancy?

DISCUSSION

DR. W. B. COHEN, Providence: I wish to offer the diagnosis of benign juvenile melanomas associated with xeroderma pigmentosum.

DR. MALCOLM WINKLER, Providence: My experience with malignant melanomas has been that the clinical course with respect to the time factor is most unpredictable and unexplainable. I have seen the report of a case in which a surgeon excised a malignant melanoma widely, 5 in. (12.7 cm.) on all sides, and deeply, the removal being followed by metastases to lymph nodes, etc., within one week. In other reported cases 10 or 20 years have elapsed before metastasis. Of course, in the latter cases the relation to original lesions remains to be proved. The present case probably will show metastases sooner or later.

DR. V. J. RYAN, Providence: It is interesting that these lesions could be controlled by extensive fulguration. In my opinion these lesions were not malignant melanomas. It is impossible at times to differentiate clinically between the benign and the malignant melanoma. I have always been reluctant to use fulguration for any lesion of this type. I still feel that if therapy is to be instituted, it should be wide surgical excision. Seldom does one have the opportunity to study a case of this sort over a period of so many years.

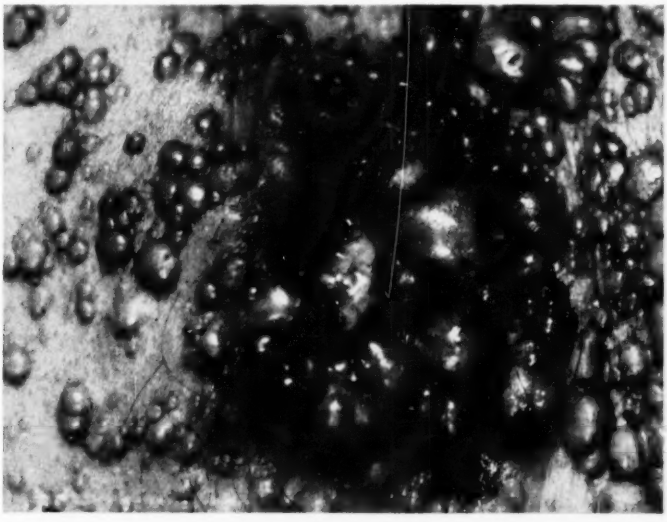
DR. B. L. SCHIFF, Pawtucket: In the absence of general metastasis, 11 years after the appearance of the first lesion, I should consider the melanomas to be of low-grade malignancy. The possibility of delayed metastasis, if such a term can be used, might be considered in this case. One would expect the carcinoma developing in xeroderma pigmentosum to be of basal-cell or squamous-cell type. I believe that benign forms of xeroderma pigmentosum, although rare, do exist. Cases have been reported in the literature in which victims have attained the age of 50, instances which should prove the point. The consensus of dermatologists is that once the diagnosis of malignant melanoma is made, wide excision of the lesion by surgery or surgical diathermy should be accomplished. Whether or not it is the treatment of choice further clinical observations would reveal.

DR. F. RONCHESE, Providence: The problem of how to handle pigmented tumors is well discussed in two recent papers (Stegmaier, O. C., and Montgomery, H.: Histopathologic Studies of Pigmented Nevi in Children, *J. Invest. Dermat.* **20**:51 [Jan.] 1953. Shaw, C.: Benign Pigmented Nevi: A Survey of Treatment of Dermatologists, *South. M. J.* **46**:286 [March] 1953) and in a comment to an answer to a query (Hall, A. F.: Dark Brown Mole, Queries and Minor Notes, *J. A. M. A.* **152**:776 [June 20] 1953).

Angioneurotic Edema of the Nose. Presented by DR. B. L. SCHIFF, Pawtucket.
Prickle-Cell Carcinoma. Presented by DR. V. J. RYAN, Providence.
Parapsoriasis Guttata. Presented by DR. A. B. KERN, Providence.
Seborrheic Eczema. Presented by DR. W. B. COHEN, Providence.
Acquired Nail Deformity. Presented by DR. F. RONCHESE, Providence.
Urticaria Pigmentosa. Presented by DR. A. B. KERN, Providence.

Neurofibromatosis and Adenocarcinoma of (Male) Breast. Presented by DR. F. RONCHESE, Providence.

A man aged 75 with extensive Recklinghausen's disease (neurofibromatosis) came to Rhode Island Hospital tumor clinic because of a fixed, deeply ulcerated area corresponding to the left breast. The necrotic area fluoresced a vivid red under the Wood light, characteristic of epidermoid carcinoma. The biopsy report was adenocarcinoma of the breast. Because of fixity, extension, and metastasis, the lesion was considered inoperable, and it was treated by orchiectomy. After four weeks the fluorescence was reduced practically to nil, and the lesion was showing



Adenocarcinoma of the breast in a 75-year-old man with Recklinghausen's disease.

involution. Diminution or disappearance of the red fluorescence can be considered eventually as a sign of a favorable effect of the orchiectomy.

DISCUSSION

DR. B. L. SCHIFF, Pawtucket: I would suggest that roentgenograms be taken to detect bone involvement. Dr. Ronchese should be commended for developing a new diagnostic aid in cancer detection with the Wood light filter. This case showed how sensitive this diagnostic aid may be.

Blue Nevus. Presented by DR. F. RONCHESE, Providence.

Solar Dermatitis(?). Presented by DR. M. WINKLER, Providence.

Lupus Vulgaris After Plastic Surgery. Presented by DR. V. J. RYAN, Providence.

Nodular Vasculitis. Presented by DR. B. L. SCHIFF, Pawtucket.

Glossitis Rhomboidea Mediana(?). Presented by DR. V. J. RYAN, Providence.

Mongolian Spot on Shoulder. Presented by DR. F. RONCHESE, Providence.

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Feb. 20, 1953

Localized Scleroderma in Father and Daughter. Presented by DR. REES B. REES, and DR. JAMES BENNETT.

E. A., a salesman aged 53, has atrophic pigmented lesions on the left side of his back and left side of his forehead and scalp. The first lesion appeared about 15 years ago on his back, and the condition has been slowly progressing. The lesion on the upper trunk appeared in the past two years and is extending more rapidly than the previous ones. He first sought medical care on Dec. 5, 1952, and his only medication has been a histamine ointment.

On the left side of his back are three palm-sized, atrophic pigmented lesions with telangiectasia. The middle lesion extends beyond the midline. There are scattered papular areas within the lesions, which represent lobules of fat beneath the atrophic skin. In addition, he has an *en coup de sabre* lesion in the left paramedial aspect of his forehead which extends to his hair line. In the left frontal area of his scalp are two atrophic, depressed lesions with alopecia.

R. A., his daughter, aged 11, has two palm-sized, depressed lesions on the left side of her back, which first appeared about one year ago. They resemble and are in the same location as those on her father's back. She is not presented at this meeting, but a Kodachrome slide of her back is available. Her lesions are apparently stationary at present. Her treatment has included administration of tolazoline (Priscoline) tablets, concentrated vitamin D (Ertron) capsules, and a histamine ointment.

DISCUSSION

DR. EUGENE FARBER: Until tonight I have never seen morphea in a parent and a child. This does not prove that there is a familial factor in localized scleroderma. Rather, this occurrence should be considered as a rare coincidence. There is no evidence of hemiatrophy of the forehead, and I should regard the lesion on the forehead as a solitary patch of morphea and should not expect a hemiatrophy to develop, as it frequently does with the *coup de sabre* lesion.

DR. MAYNARD: I was impressed by the unilateral intercostal distribution of these lesions in the father and daughter. At a meeting of this Society about 20 years ago I presented a patient in whom scleroderma had followed herpes zoster in the precise area of the zoster. X-ray pictures of the spine should be taken in such cases to determine whether there is a developmental abnormality that might account for this unusual change. The psychiatrist may say the daughter identifies with the father.

DR. REES B. REES: Previously I have not seen more than one case of scleroderma in a family. I believe that both these cases represent abortive hemiatrophy. Wartenberg has stressed that all cases of saber-cut scleroderma of the forehead are actually instances of abortive hemiatrophy. The lesions in these two cases are unilateral, although in the father one of the lesions on the upper back extends partially across the midline. His process has ended in atrophy.

Arsenical Keratoses and Squamous-Cell Carcinoma in a Man of 25 Years. Presented by CAPT. JOHN P. BRISKE, Medical Corps, United States Army (by invitation).

Parakeratosis Variegata? Presented by DR. EDWARD J. RINGROSE.

Nevus Unius Lateris. Presented by DR. C. J. LUNSFORD.

Pityriasis Lichenoides et Varioliformis Acuta. Presented by DR. H. V. ALLINGTON.

Idiopathic Telangiectasia. Presented by COL. ROBERT S. HIGDON, Medical Corps, United States Army.

Relapsing Febrile Nodular Nonsuppurative Panniculitis. Presented by DR. MORTIMER S. FALK.

Case for Diagnosis: Tuberculosis of the Skin? Sarcoid? Presented by DR. ERVIN EPSTEIN and DR. JOSEPH P. BELBER.

Circumscribed Myxedema. Presented by LIEUT. V. J. SLOMINSKI, Medical Corps, United States Army.

Balanitis Xerotica Obliterans. Presented by DR. WILLIAM F. B. HARDING.

Papular Amyloidosis Cutis. Presented by DR. ARNE ELY INGELS.

Juvenile Melanoma. Presented by DR. ARNE ELY INGELS.

Leucoderma Acquisitum Centrifugum. Presented by DR. H. L. JOSEPH.

News and Comment

ANNOUNCEMENTS

Prize Essay Contest in Dermatology.—The American Dermatological Association will award cash prizes ($500, $300, and $200) for the best essays submitted for original work, not previously published, relative to some fundamental aspect of dermatology or syphilology. Competition is open to scientists generally, not necessarily to physicians. Manuscripts, typed in English with double spacing and ample margins as for publication, together with illustrations, charts, and tables, all of which must be in triplicate, are to be submitted not later than Dec. 1 to Dr. J. Lamar Callaway, Secretary, American Dermatological Association, Duke Hospital, Durham, N. C. Results will be announced before Jan. 1, 1954. The candidate winning first prize may be invited to present his paper before the annual meeting of the American Dermatological Association (April 13-17, 1954, at the Greenbrier Hotel, White Sulphur Springs, W. Va.), with expenses paid in addition to the $500 prize.

Books

Dermatological Formulary. By Ashton L. Welsh. Revised. Price $4.50. Pp. 275. Educational Publishers, Inc., 122 N. 7th St., St. Louis 1, 1952.

This practical little book is divided into three sections. The first, containing 68 pages, deals with topical therapy; the second, containing 160 pages, deals with those drugs which are administered internally, while the third, and last, section, containing 43 pages, deals with miscellaneous subjects, such as prescription writing, diets, and stain removers, and includes a manufacturers' and distributors' index.

Almost all the therapeutic agents used by modern-day physicians are mentioned in one place or another in the book. In his foreword, the author intimates that he does not expect the dermatologist to prescribe those medications which fall within the realm of other medical specialties, yet he seems to suggest in certain discussions that the dermatologist could do so with the information given in this book if he should choose. In this sense the book overreaches itself.

However, there are several qualities in the book which give it unusual practical value. For one, the various trade names under which drugs are marketed are listed briefly wherever it may be of importance. This is the sort of information which can be invaluable to a busy practitioner. For another, the capsulized pharmacological discussions are, in certain cases, brief and accurate, just what is needed to sharpen one's memory as to the properties and indications for use of any given drug. The section on topical therapy is handled with a minimum of confusion and is well done.

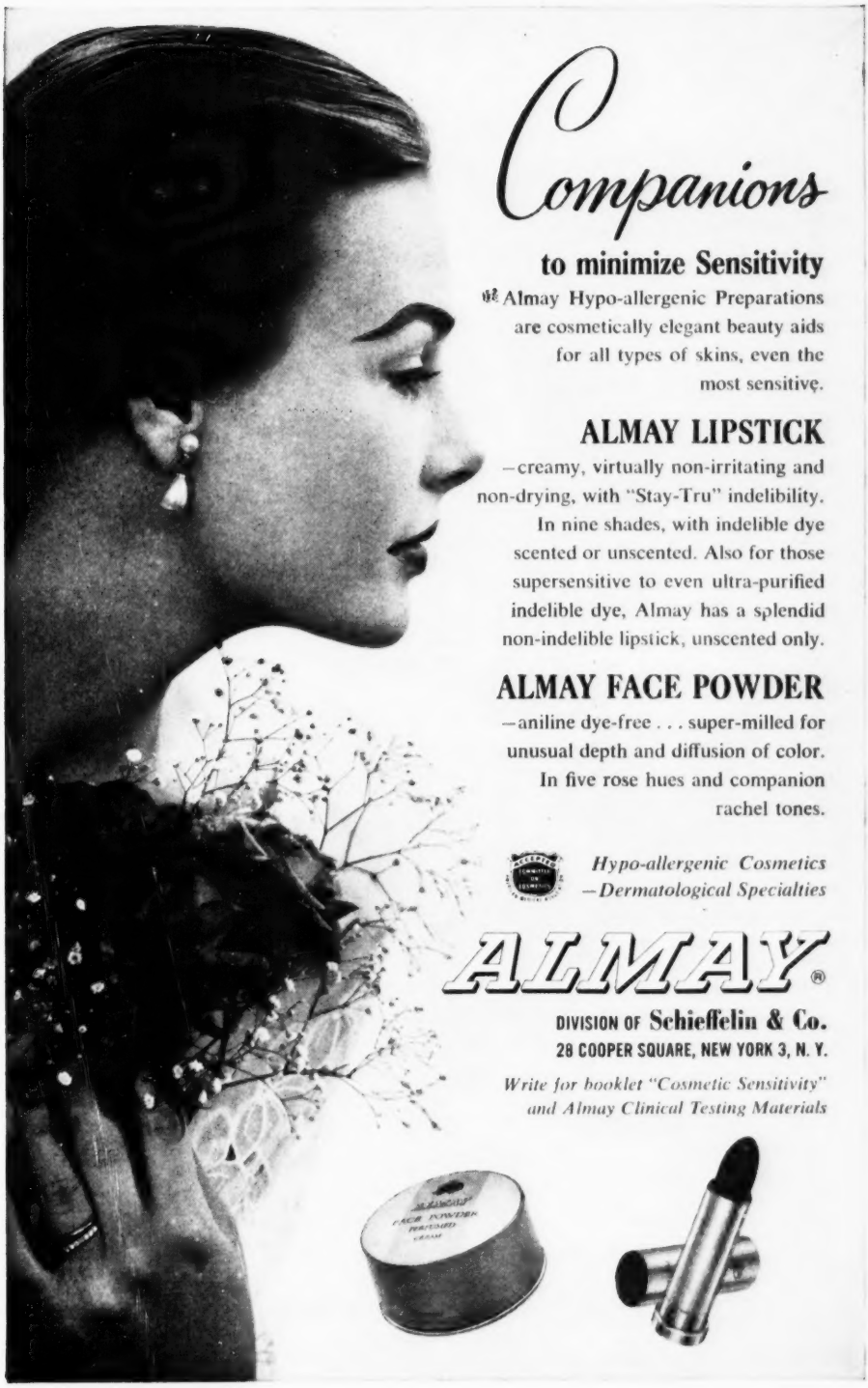
This volume was written originally for the use of the medical students and the staff of the Cincinnati General Hospital, but in the opinion of this reviewer it is destined for a wider audience and a longer life than its author may have intended.

Emotional Factors in Skin Diseases. By Eric Wittkower and Brian Russell. Price $4.00. Pp. 214. Paul B. Hoeber, Inc., 49 E. 33d St., New York, 1953.

To the dermatologist who is interested in the etiology of skin diseases this book will be a disappointment. The authors, a dermatologist and a psychiatrist, studied the personalities and emotional backgrounds of persons with seborrheic dermatitis, psoriasis, alopecia areata, rosacea, acne vulgaris, alopecia, a history of eczema in the family, and pruritis vulvae et ani. The end of each chapter includes a brief summary of the outstanding characteristics of the psychosomatic histories of the group studied.

The relationship between the psychosomatic states and the skin conditions as brought out in this book are not impressive. To this reviewer, the loose statements and the verbalism fail to establish an etiologic relationship between the skin lesions and the psychosomatic state. As an example, the authors say that "alopecia may have many causes: one of them which has been underated and imperfectly understood is the effect of emotional disturbances," and later that "only one case of alopecia areata and none of alopecia totalis was found in a psychotic population of 13468."

Emotional states aggravate some skin diseases and many skin diseases disturb the emotional state, but this book offers little proof that the diseases studied were caused by the patient's psychosomatic state.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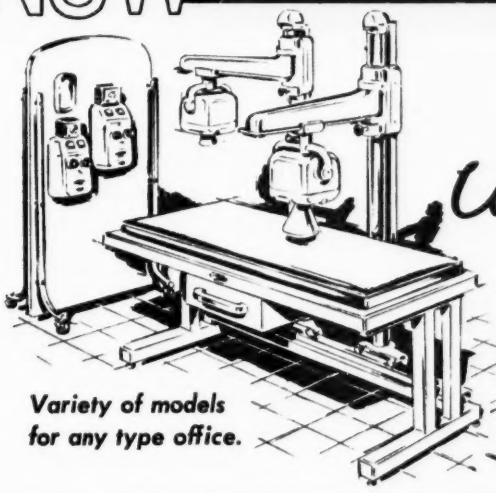

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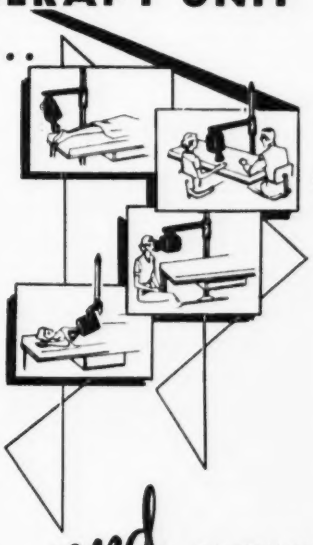

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*Sulzberger, M. B., and Wolf, J.: Dermatology, Essentials of Diagnosis and Treatment, Chicago, Year Book Publishers, Inc., 1952, p. 323.

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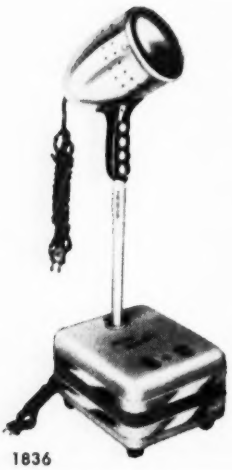

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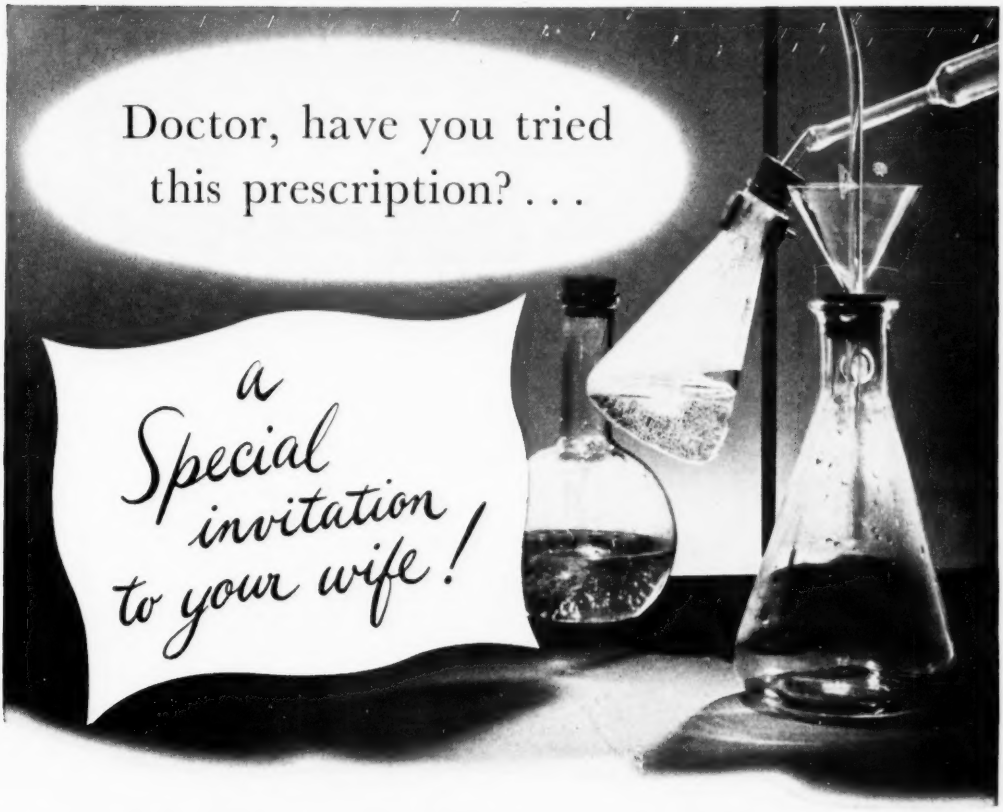

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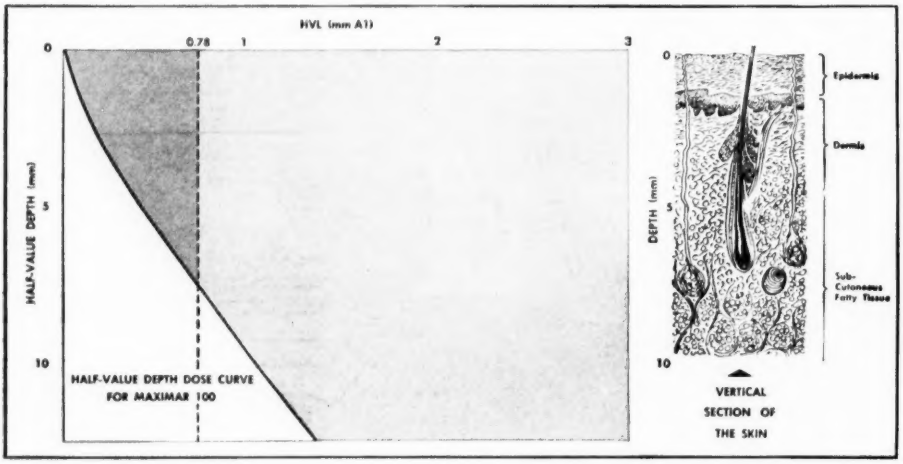

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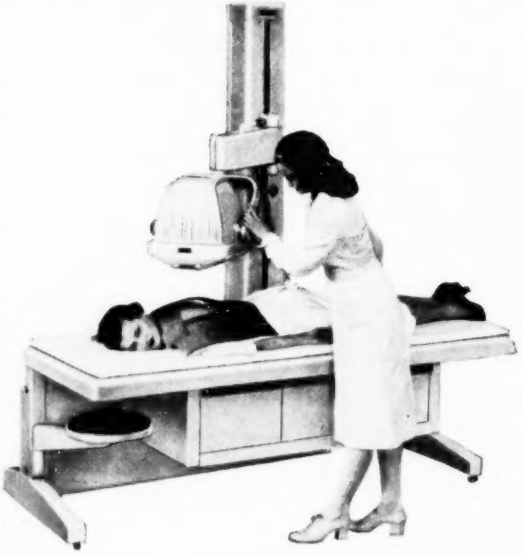

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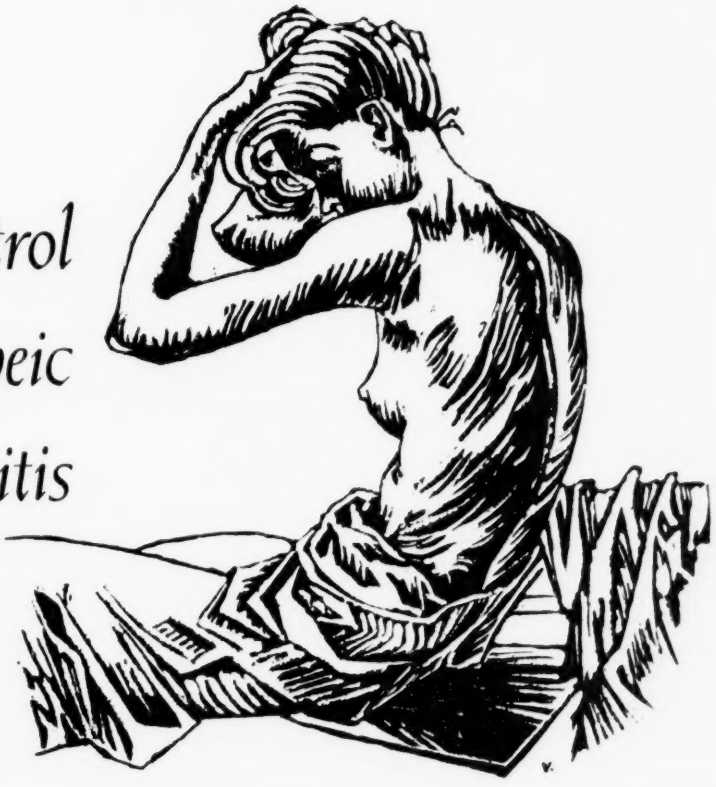

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1. Slepyan, A. H. (1952), Arch. Dermat. & Syph., 65:228, February.
2. Slinger, W. N., and Hubbard, D. M. (1951), *ibid.*, 64:41, July.
3. Sauer, G. C. (1952), J. Missouri M.A., 49:911, November.